Basics of radiopharmacy

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with 246 illustrations, including drawings by Mark Prouse

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Foreword

The evolution of radiopharmacy as a specialty has been extremely rapid when compared to other disciplines within pharmacy. Essentially it has developed as a specialty area within a period of 20 years, and its route has been tortuous. The preparation, dispensing, and clinical investigation of radioactive materials as drugs started experimentally early in the 1950s with the use of ^{131}I and ^{32}P. As the early use of these and other nuclides evolved and as the importance of labeled compounds as imaging agents became recognized, primary development of radiopharmaceuticals lay with the research radiochemist and physician. In the late 1960s and early 1970s, however, nuclear medicine developed as a separate medical specialty and began to expand dramatically. With this development came a whole regiment of new radiopharmaceuticals. The proliferation of these radioactive imaging agents required the parallel development of specialists qualified to prepare, run quality control on, run clinical studies on, and dispense these agents. In short, by evolution radiopharmacy and the radiopharmacist emerged as an essential discipline and as a partner to nuclear medicine and the nuclear medicine physician.

Today radiopharmacy is viewed as a distinct discipline. While constant interaction and close cooperative ties between the nuclear medicine physician and the radiopharmacist are essential, the functions of radiopharmacists are becoming more defined, and their distinct role as clinicians and as distributors of radiopharmaceuticals is evolving rapidly.

Even as the discipline of radiopharmacy develops, its future will be molded by many internal and external forces and pressures. These pressures include federal regulatory actions concerning radiopharmaceuticals, actions of state boards of pharmacy concerning radiopharmacies and radiopharmaceuticals, new directions of research in imaging in nuclear medicine, new directions in radiopharmaceutical development, and the numbers and direction of educational programs in radiopharmacy by colleges of pharmacy. It is certain that these forces and pressures among others will dictate many dramatic changes and developments within radiopharmacy in the forseeable future.

With their extensive experience in and knowledge of the field of radiopharmacy, the authors of *Basics of Radiopharmacy* have clearly defined the functions and types of professional activities that the radiopharmacist performs. This textbook provides a current and detailed description of the basics of radiopharmacy and the essential knowledge base needed for the student intending to enter this field. It also will serve as an important reference book for educators and others who wish to expand their knowledge of radiopharmacy but who may not be actively involved in practice. I congratulate the authors on a very complete text, well organized and well written. This text should be a valuable addition to the exciting and interesting new specialty of radiopharmacy.

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Preface

Basics of Radiopharmacy was written to provide a first-course textbook in radiopharmacy for use by undergraduates in pharmacy and nuclear medicine technology. The text is planned as a comprehensive introduction to the preparation and clinical use of radioactive tracers. Tracer principles are combined with pharmacy techniques to provide the student with the information needed to prepare radioactive substances for intravenous administration to patients.

The text assumes that the student will have an understanding of chemistry and basic atomic physics. Although knowledge of these subjects is assumed, an outline of prerequisite knowledge is given in the Appendix. Our experience in teaching this class over the past years is that a few review sessions are sometimes necessary to prepare the students for this course.

The outline of material was developed from courses presented at the University of Virginia, The Johns Hopkins Medical Institutions, the University of Kansas, and the University of New Mexico.

Buck A. Rhodes
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What is radiopharmacy?

Definitions

RADIOPHARMACY

A radiopharmacy is the place where radioactive drugs are prepared and dispensed. The radiopharmacy also serves as a depot for the storage of radioactive materials and nonradioactive supplies. It is here that the inventory records of radioactive materials are recorded and stored. This latter function includes the maintenance of prescription records. The radiopharmacy is also likely to be the correlation point for radioactive waste materials and their assignment to waste disposal or waste storage units.

The radiopharmacy is usually a center for clinical investigations employing radioactive tracers, as well as for education of radiopharmacy students, nuclear technology students, and nuclear medicine or radiology residents. The radiopharmacy may also be a center for research in the development of new radioactive tracers.

We often divide the work of the radiopharmacy into two primary activities, dispensing and clinical. The dispensing function is considered first. This includes all activities required to prepare and deliver to the clinic the radioactive tracers needed for patient studies. Usually, multidose amounts of several tracers are prepared each morning. Calculations to correct for radioactive decay are used to determine how much of a tracer is to be measured out for an individual patient. Not only must the amount of the tracer, in terms of *millicuries* (mCi) or *microcuries* (μCi) of radioactivity, be considered, but the amount in terms of both milligrams and milliliters must also be considered. A check system is used to assure that the dispensed drug is in the final dosage form appropriate for administration to the patient.

When a prescription is to be filled, the required amount of the stock solution is apportioned. Usually this means withdrawing a tracer solution from a lead-shielded vial into a syringe of the required size. The syringe must be fitted with the type and size of needle required for the injection. It or its carrier must be labeled with the patient's name and the dosage information: radiopharmaceutical, radioactivity calibration time, and date. As soon as the syringe is filled with the radioactive tracer and its radioactivity is measured, it is inserted into a syringe shield or syringe carrier so it can be transported to the patient without exposing anyone to the emitted radiation.

At other times, capsules are counted out, or oral solutions are measured out, into disposable cups or other suitable containers. This also requires assay of the radioactivity, labeling the dose, and housing it in radiation shields for transportation to the patient. In some instances the patient is brought into the radiopharmacy so the tracer can be administered to the patient by the radiopharmacist or technologist. Often this is the safest way to administer oral solutions of radioiodine used for therapy. Fig. 1-1 shows examples of doses of radiopharmaceuticals as they are issued by a radiopharmacy.

Radiopharmacies also may issue some nonradioactive drugs, such as perchlorate, atropine, iodide solution, or intrinsic factor. These ancillary drugs are used to enhance the uptake, alter the biodistribution, or otherwise aid in controlling the biorouting of the radioactivity.

Standards used in the calibration and quality

Syringe carrier

Vial holder (PIG)
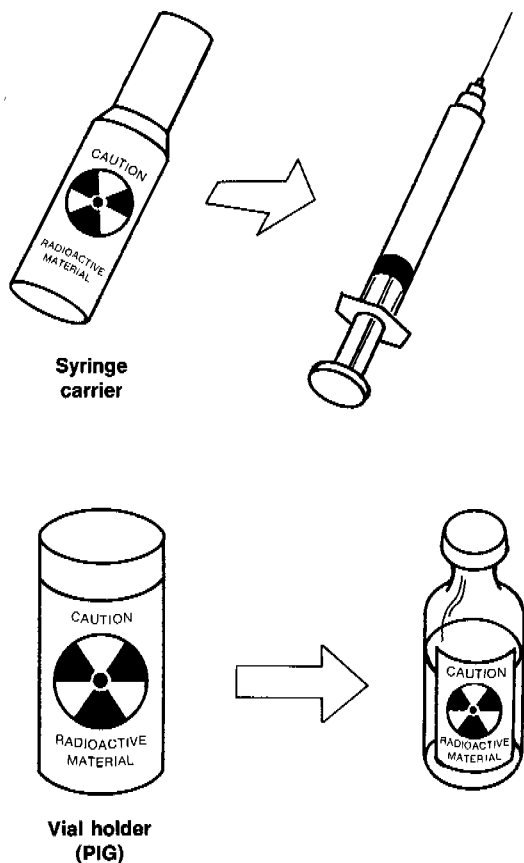
Fig. 1-1. Radiopharmaceuticals are dispensed either as unit doses (top) or as multidoses (bottom). Unit doses are usually dispensed as precalibrated ready-to-inject intravenous preparations. Multidose solutions usually contain a day's supply of radiopharmaceutical, which may be as many as ten or more doses for a busy nuclear medicine clinic.

Fig. 1-2. Field flood test source that can be loaded with ^{99m}TcO$_4^-$ solution. In background is a bar phantom. These testing devices are used for routine quality control testing of an Anger camera. (From Rhodes, B.A., editor: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.)

control testing of nuclear detection instrumentation are often stored in the radiopharmacy and issued periodically for instrument testing. For example, a field flood test source (Fig. 1-2), used to measure the uniformity of response of an Anger camera to radiation, may be loaded daily with several millicuries of pertechnetate (^{99m}TcO$_4^-$) solution and issued on request.

The radiopharmacy is responsible for quality control of the radiopharmaceuticals. The routine preparation procedures often incorporate quality control tests for radiochemical purity. For instance, most technetium-labeled com-

pounds can be tested in a matter of minutes to determine percent of radioactivity in the desired chemical state (often called *percent tag*). The effective clinical use of radiopharmaceuticals often requires understanding and communication of the quality control data. This leads us into a discussion of the clinical activities of a radiopharmacy. The clinical activities of a radiopharmacy are not really distinct from the dispensing activities; however, for simplicity of discussion the clinical activities are considered separately.

When the **biodistribution*** of a tracer is distributed in the patient in a manner that is unexplained by the patient's pathology or differs significantly from what is normally expected, then the performance of the tracer becomes suspect. In order to proceed with the diagnosis, the nuclear medicine physician frequently requires additional information obtained from quality control or other types of performance tests. Sometimes this may involve talking with

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*Terms in boldface are defined in the Glossary.

the patient to determine drug history, checking the results of other patients who have been given the same tracer, and may even require doing tissue distribution studies in animals. These troubleshooting activities make up a part of what is called clinical radiopharmacy.

In summary, a radiopharmacy is a dispensary where orders for radioactive drugs to be used in patients are filled. *Supply of radioactive drugs and troubleshooting of radioactive tracer studies are major radiopharmacy functions.*

RADIOPHARMACEUTICALS

What is a radiopharmaceutical? The term that is legally defined in the *Federal Register of the U.S.A.* is *radioactive drug.* This is any substance defined as a drug* in the federal Food, Drug, and Cosmetic Act that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of any such substance.

The term radioactive drug includes *radioactive biologic product.* Carbon- and potassium-containing compounds with naturally occurring ^{14}C and ^{40}K are excluded from this definition.

Basically, radiopharmaceuticals are usually classified as diagnostic (rad D_x), therapeutic (rad R_x), or research radiopharmaceuticals. They can also be classified by reference to the categories that stem from the legal definition of a radioactive drug. These classes and examples are listed in Table 1-1.

Diagnostic radiopharmaceuticals. These are radioactive drugs used for diagnostic purposes as radioactive tracers in patients. These drugs broadcast their positions within the body by their gamma-ray emissions. By monitoring

Table 1-1. Classification of radioactive drugs

Type	Examples
Multidose—commercially supplied	^{131}I Rose Bengal, technetium 99m solution, U.S.P.
Generators	$^{99}Mo/^{99m}Tc$ generator
Reagent kits	Kit for preparing ^{99m}Tc pyrophosphate

these broadcasts we can infer the concentrations of the tracer material in different organs. Using the signals, we can even obtain low-resolution images of the organs. By monitoring these broadcasts as a function of time, we can study the kinetics and metabolism of the drug within the body. The monitoring device is usually a **collimated** external gamma-ray detector. Thus, diagnostic radiopharmaceuticals are administered to patients to differentiate normal from abnormal biochemistry, physiology, or anatomy.

Unfortunately, not all diagnostic radioactive tracers are gamma emitters that permit their **in situ** determination with noninvasive external radiation detectors. A few diagnostic radiopharmaceuticals are prepared using tritium, carbon 14, or phosphorus 32. Since these **isotopes** do not emit gamma rays, it is impossible to monitor their position within the body using external detectors. They can be used, however, in tracer diagnosis by taking samples for analysis. One example of this is to administer glucose ^{14}C and then monitor the excretion of carbon dioxide ^{14}C in the breath as an indicator of the absorption of the compound, its subsequent metabolism, and its elimination in the breath as the metabolic end product, $^{14}CO_2$. Other body fluids that can be sampled and counted are blood, urine, and, in some instances, biopsy samples.

Therapeutic radiopharmaceuticals. Radioactive substances can be administered to a patient for the purpose of delivering radiation to body tissues internally. The best example of this is the administration of iodide 131 for the purpose of thyroid ablation in patients who are hyperthyroid. The thyroid is internally irradiated by the radioactive iodine that it concentrates.

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*The term *drug* means (1) any of the articles recognized in the official *United States Pharmacopeia,* official *Homeopathic Pharmacopeia of the United States,* official *National Formulary,* or any supplement to any of them; (2) an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; (3) an article (other than food) intended to affect the structure of any function of the body of man or other animals; and (4) an article intended for use as a component of any articles specified in clause 1, 2, or 3; the term does not include devices or their components, parts, or accessories.

Fig. 1-3. Radiopharmacist answers telephone, taking prescription for radiopharmaceutical. Prescription is typed from information received over telephone.

Fig. 1-4. Dose of radiopharmaceutical is withdrawn from vial in lead container into syringe. Radiopharmacist works behind lead shield and observes work through leaded glass window shield.

Other radiopharmaceuticals that are used for therapeutic purposes are those administered in the treatment of certain cancers.

Regular drugs labeled with a radioactive tracer. Another type of radiopharmaceutical is a regular drug labeled with a small quantity of radioactive substances. These are administered to the patients, not for diagnostic purposes, but to study the metabolism and kinetics (i.e., the biodistribution) of a drug that may eventually be used in a nonradioactive form. This type of radiopharmaceutical is used primarily for research purposes.

RADIOPHARMACISTS

Radiopharmacists are responsible for the filling and dispensing of prescriptions for radioac-tive tracers and for the clinical aspects of radio-pharmacy. In order to carry out these functions, radiopharmacists need to be trained in (1) ra-dioactive tracer techniques, (2) safe handling of radioactive materials, and (3) preparation and quality control of drugs prepared for adminis-tration to humans. These individuals are also required to understand the basic principles of nuclear medicine so that they can function ef-ficiently when troubleshooting clinical prob-lems involving performance failure of the radioactive tracer in an individual patient (Figs. 1-3 to 1-5).

The first radiopharmacists usually were not pharmacists, but individuals who were involved in the creation of the specialty of nuclear medi-cine, individuals who were interested in the
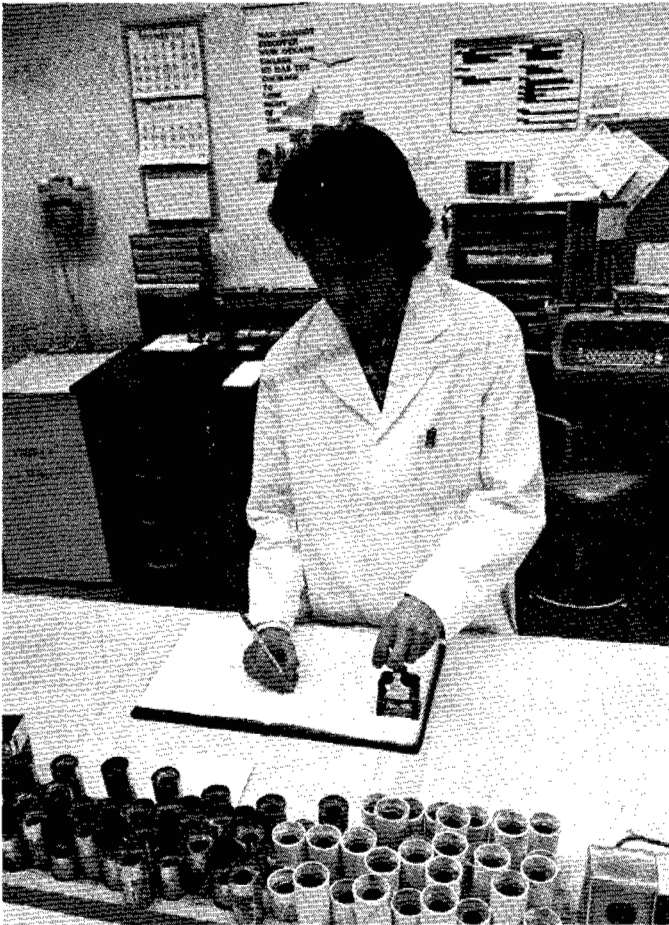
Fig. 1-5. Each prescription is numbered serially and recorded in master log. Each patient dose must be traceable to vial from which dose was drawn, to quality control test data, and to supply of radioactive material used in its formulation.

application of tracer techniques to the diagnosis and management of patients. Many of these individuals came from related areas of science such as chemistry, radiochemistry, physics, chemical engineering, and biology. Their training usually included few formal courses, with most of the training being on the job. This training dealt primarily with the handling of radioactive materials and the application of tracer techniques to diagnostic problems. These individuals were forced to learn aseptic techniques in order to be able to prepare these new tracers for administration to patients.

Currently, it is widely appreciated that some of the best candidates for becoming a radiopharmacist are persons trained in pharmacy, then trained in the special techniques of radiolabeling drugs. Some states require that radioactive drugs be dispensed by a licensed pharmacist. Other states recognize individuals called radiopharmaceutical specialists who may or may not be graduates of a school of pharmacy. In many institutions the individual who prepares the radiopharmaceuticals works under the direct supervision of a nuclear medicine physician, who may assume the primary legal responsibility for the safety and efficacy of the drugs that are administed to patients, thus obviating the requirement to have a registered pharmacist dispensing the radiopharmaceuticals.

NUCLEAR MEDICINE

Nuclear medicine is a specialty devoted to the diagnostic and therapeutic use of radioactive compounds. The application of radioactive tracer technqiues in the study of human biology began in the early 1920s. George de Hevesy's classical volume, *Radioactive Indicators,* set forth many of the basic principles that were later incorporated into the nuclear diagnostic techniques. Herrman Blumgart was one of the first individuals to apply natural radioactive isotopes in the study of circulation in man. Artificial radioactive isotopes were introduced at first by E. O. Lawrence around 1932. In 1946 the Atomic Energy Commission was established by Congress; a significant area of focus was the peaceful use of atomic energy

in medicine. The supply of radioactive isotopes rapidly expanded with the development of nuclear reactors that followed World War II. Programs were instituted both nationally and internationally to promote the peaceful uses of atomic energy. Many of the early studies were encouraged and funded by these programs. Since that time, nuclear medicine has become a vital part of the diagnostic and therapeutic management of patients. Since 1971, the Joint Commission for Accreditation of Hospitals has required that a nuclear medicine service be present or at least that formal arrangements be made to provide these services to patients in order for a hospital to receive accreditation. By 1975, approximately 50% of the nation's hospitals had some type of nuclear medicine facility. It is projected that some 20 million studies will be conducted annually by 1980.

Nuclear procedures are useful for a broad range of disease states. At least 15% of all patients admitted to a hospital will have a nuclear medicine procedure as part of their routine diagnostic workup. The spectrum of diagnostic procedures includes (1) **static imaging** of organs and compartments, (2) **sequential** or **functional imaging** of physiologic processes, (3) **in vivo** tracer studies (Fig. 1-6), and (4) **in vitro** studies.

In 1971 the American Board of Nuclear Medicine was approved by the American Medical Association Council on Medical Education and the American Board of Medical Specialties. A physician, after fulfilling one of several accepted combinations of training and experience, can become qualified for examination by the specialty board. On satisfactory completion of the examination he is admitted into the specialty as a board-certified nuclear medicine physician. Beginning in 1977, a physician must have completed an approved residency program to become eligible to apply to take the certifying examination.

Nuclear medicine is interdisciplinary in nature and relies heavily on interactions with all medical specialties. Input into the development of this field comes from continuing advances in electronics, computer science, physics, analytical chemistry, nuclear chemistry, and radiopharmacy.
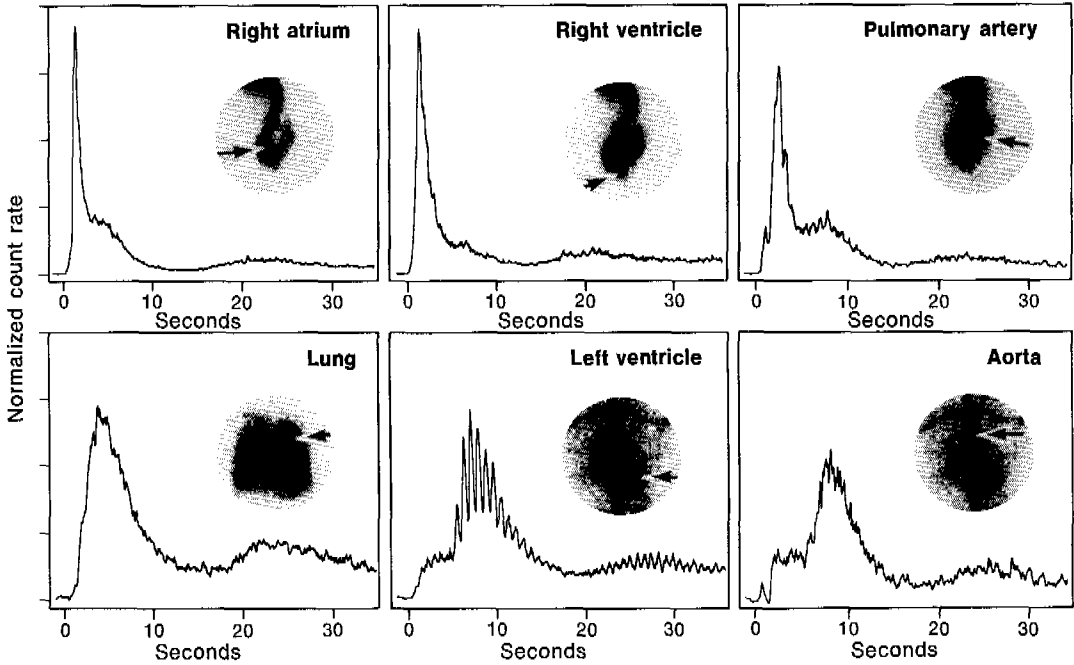
Fig. 1-6. This *in vivo* tracer study is a radionuclide angiocardiogram. Strip-chart recordings show passage of radioactive tracer through six areas of interest in central circulation. Arrows indicate anatomic structure selected for each recording. (From Van Dyke, D. C., Anger, H. O., Sullivan, R. W., Vetter, W. R., Yano, Y., and Parker, H. G.: J. Nucl. Med. **13**:585-592, 1972.)

History of radiopharmacy

Before radiopharmacy there was *bionucleonics*. This term was used as a catchall title for courses taught in colleges about the biologic application of radioactive materials. In these courses, the use of radioactive tracers in the study of physiology, chemistry, and biology was discussed. The courses also dealt with nuclear physics, nuclear instrumentation, radiochemistry, and radiation safety. As the use of radioactive indicators as diagnostic agents became more widespread, the courses were expanded to include a bit of pharmacy, particularly instruction in the use of **aseptic** procedures and other techniques associated with the preparation of **intravenous** solutions.

Programs were initiated by several national laboratories, which made major contributions to the development of the clinical use of radioactive materials. As these laboratories began to produce radioisotopes, they developed both training programs in their medical applications and undertook basic research that provided much of the basic data needed to develop the tracer techniques.

Of major importance was the work done at Oak Ridge, Tennessee. In 1946 the Oak Ridge National Laboratory began to produce radionuclides for biologic and medical purposes. These were made in an air-cooled graphite nuclear reactor. Many physicians and biomedical scientists who have contributed the foundations to this field began by training and working at Oak Ridge.

National laboratories in other nations also began to supply reactor-produced nuclides for biomedical purposes and to conduct training programs.

The International Atomic Energy Agency has been an active force in the formalization and evolution of the field of radiopharmacy. In 1966 the agency published the *Manual of Radioisotope Production*. The agency sponsored several study groups and international symposiums, published several monographs, and in 1971 revised their original manual and published

rose bengal, an indicator of liver function. Iodine can be tagged to almost any protein. One of the most widely used is human serum albumin; radioiodinated human serum albumin can be used as a tracer of plasma proteins. It can be **microaggregated** to form a colloidal particle, which can be used to visualize the reticuloendothelial system, and **macroaggregated** to produce an indicator of relative regional perfusion to the lungs. Iodine 131, which is a satisfactory isotope for therapy, is far from ideal for use as a diagnostic tracer because of its long half-life, its high-energy beta radiation (has high-radiation exposure), and the possibility of the radioactive element concentrating in normal thyroid tissue and causing long-term radiation damage to the gland. Iodine 131 has been popular for many years because it is cheap and widely available. It can be used to prepare radioactive tracers with long shelf-lives; thus, the material can be prepared in one area and shipped for use in distant hospitals. The radiochemistry of iodine became well understood, and radiochemists have become quite adept at incorporating this tracer atom into a wide variety of molecules.

Probably the greatest impetus to the development of radiopharmacy was the introduction of the ^{99m}Tc generator. Powell Richards, working at Brookhaven National Laboratory, realized the potential of the parent-daughter pair of radionuclides, molybdenum 99 and technetium 99m, in the early 1960s. In 1966 he reported the details of a generator system that would permit the short-lived ^{99m}Tc radioisotope to be made available at laboratories located great distances from the source of the parent **nuclide,** ^{99}Mo (Fig. 1-8). Soon after this, other investigators began to appreciate the potential of ^{99m}Tc and to evaluate it as a tracer in biologic systems. Since that time, a great variety of compounds have been prepared that are labeled by complex formation with reduced ^{99m}Tc. The radionuclide, as it is obtained from the generator, can be used directly as a radioactive tracer. Fortunately, the generator system can be eluted with sterile, pyrogen-free saline to obtain directly a drug of pharmaceutical quality.

Why is this radioisotope so important to the

Fig. 1-7. Patient is receiving dose of ^{131}I iodide solution, which is administered to ablate thyroid. Treatment is used for hyperthyroidism and thyroid carcinoma.

the basic reference book, *Radioisotope Production and Quality Control*.

The clinical applications of radioisotopes began to gain popularity with the realization that a drink of a solution of radioiodine could be used in place of the related complicated and sometimes dangerous thyroid surgery (Fig. 1-7).

Iodine 131 was initially used for the study of iodine metabolism and for the evaluation of thyroid function, as well as for radiation therapy of the thyroid. Iodine 131 eventually became the most popular radionuclide for the preparation of radiopharmaceuticals. It was used to label sodium iodohippurate, a substance secreted by the kidneys, thus giving us an indication of renal function. It was used to label

Since radiation exposure to the patient is minimized by using shorter- and shorter-lived radionuclides, the problems of obtaining the indicator and converting it into a suitable tracer become increasingly important. The radiopharmacist of the future must not only be adept at the rapid formulation of ^{99m}Tc compounds but must also become involved in the preparation of even shorter-lived compounds prepared from such radionuclides as carbon 11 (20.4 minutes) or fluorine 18 (109.8 minutes).

A major event that helped to begin the formalization of the basic concepts of radiopharmacy was a 1966 symposium on radioactive pharmaceuticals at Oak Ridge, Tennessee. This symposium and the subsequent publication of its proceedings* documented many of the basic principles of radiopharmacy. At this time the word radiopharmaceutical had not yet been widely used. The more common terms in the early days were atomic cocktails, radioindicators, and radioactive pharmaceuticals. After considerable debate, Wagner, in his classic text *Principles of Nuclear Medicine,* agreed to use the word radiopharmaceutical, establishing this term once and for all.

Another major event contributing to the formation of this field was the First National Symposium on Radiopharmaceuticals held in Atlanta, Georgia, in February, 1974. This meeting was cosponsored by the Society of Nuclear Medicine, Inc., and the U.S. Food and Drug Administration. The purpose of this symposium was to generate comprehensive reviews of the major radiopharmaceutical categories, to present developments in radiopharmaceutical technology, to provide a forum for exchange of ideas, and to publish a comprehensive review of the field. The review book, published by the Society of Nuclear Medicine, Inc., in 1975,† provided an updated overview of the development and use of radiopharmaceuticals.

Only recently have colleges of pharmacy begun to develop training programs in radiophar-

Fig. 1-8. Powell Richards of Brookhaven National Laboratory. In 1977 Richards received the Paul C. Aebersold Award for his contributions to nuclear medicine, which include development of ^{99}Mo/^{99m}Tc generator.

development of radiopharmacy? It has a physical half-life of 6 hours. Thus, in order to use it, a ^{99m}Tc generator is eluted daily. **Compounding** of the tracer drug must occur the same day that the patient is to be studied. Either the eluate is directly used for administration to the patient, or it is subjected to radiochemical manipulation to prepare one of several other possible radioindicators. Thus, in order to run a modern nuclear medicine clinic, the daily job of obtaining the radioactive isotope and preparing it for injection into patients has become very important. At the present time approximately 85% of the 10 million or more diagnostic tracer studies performed each year in the United States require ^{99m}Tc as the basic radionuclide. The demand for high-quality drugs made with ^{99m}Tc has in turn created a demand for specialists in the handling and chemical manipulation of this radionuclide.

*Andrews, G. A., Kniseley, R. M., and Wagner, H. N., Jr., editors: Radioactive pharmaceuticals, Springfield, Va., 1966, U.S. Department of Commerce.
†Subramanian, G., Rhodes, B. A., Cooper, J. F., and Sodd, V. J., editors: Radiopharmaceuticals, New York, 1975, Society of Nuclear Medicine, Inc.
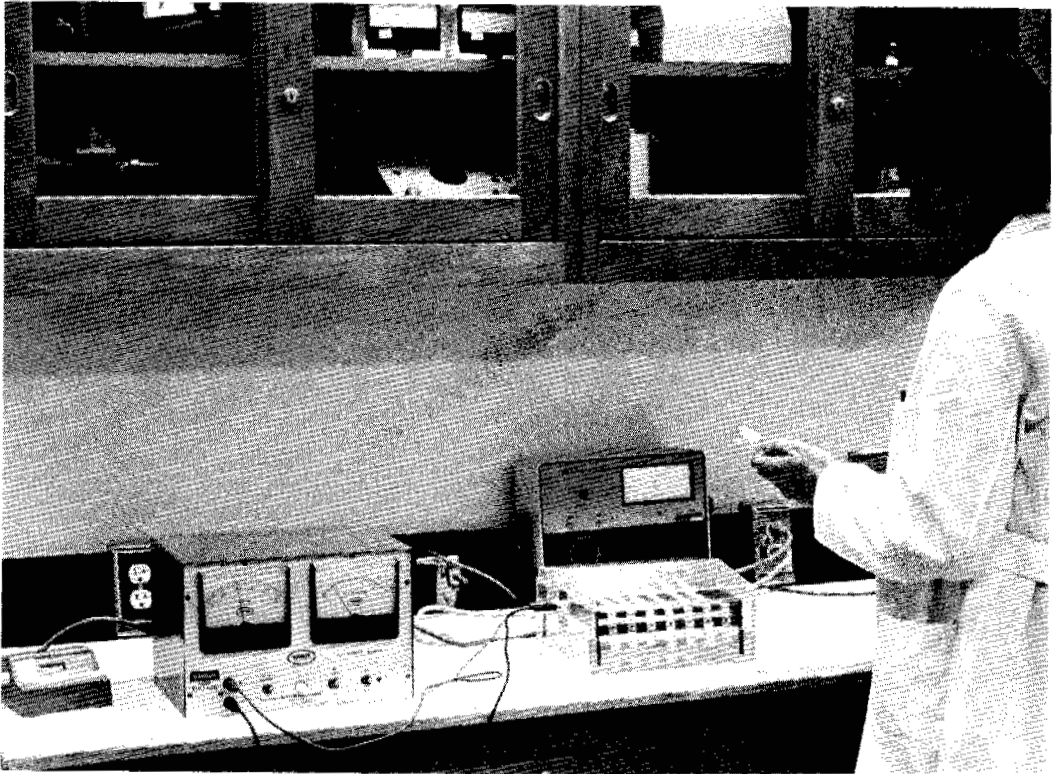
Fig. 1-9. Each formulation is tested to determine percentage of radionuclide that is in appropriate radiochemical state.

Fig. 1-10. Most radioactive tracers are administered through antecubital vein in arm.

macy. The programs that have provided most of the first radiopharmacists with formal college educations in this field are the master of science program in radiopharmacy at the University of Southern California, developed by Walter Wolf and Manuel Tubis, and the bachelor of science program (Fifth-Year Option in Radiopharmacy) at the University of New Mexico, developed by Richard Keesee and Carman Bliss.

Radiopharmacy compared to pharmacy in general

When a pharmacy student first looks at radiopharmacy, it seems to be almost a foreign subject; however, after studying and working in the field for a while, its similarities to other areas of pharmacy begin to become apparent. To help bring about this integration it is useful to examine the similarities and the differences between pharmacy and radiopharmacy.

The pharmacist deals primarily with therapeutic drugs. A radiopharmacist deals primarily with diagnostic drugs. Actually, for a tracer to be a true tracer, it must have no pharmacologic effect whatsoever. Thus, whereas a pharmacist is concerned that his drugs are producing the desired pharmacologic effect, the radiopharmacist is concerned if his drugs are producing any effects. Both are concerned with drug performance, but the tools used to measure performance of an R_x are quite different from those used to measure the performance of a D_x. Both are concerned with drug interactions; one involves changes in the therapeutic process, and the other involves change in biodistribution that influences the diagnostic process.

Fig. 1-11. Radiopharmacist is taking drug history of patient who will receive dose of ^{131}I iodide. Histories are also taken from patients who are suspected of having an adverse reaction to a radiopharmaceutical.
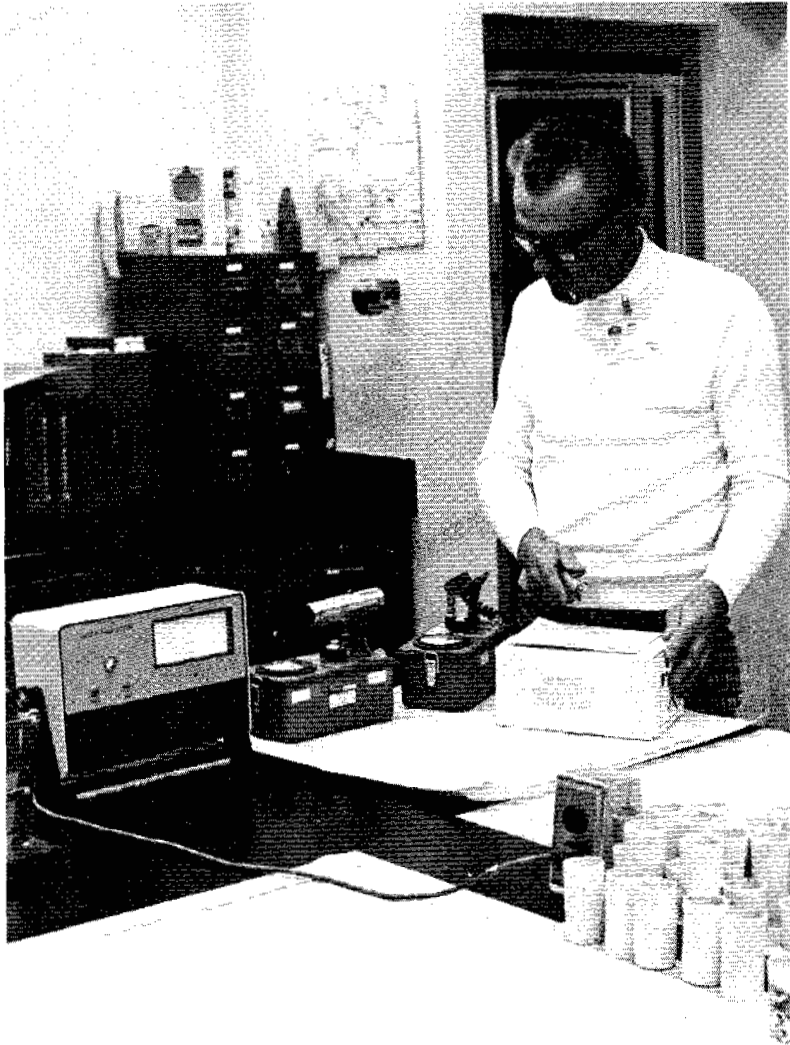
Fig. 1-12. Radioactive prescriptions are packaged in lead-carrying shields according to U.S. Department of Transportation regulations and surveyed prior to leaving central radiopharmacy.

Most pharmacists compound only a few of the drugs they dispense; a radiopharmacist will probably compound at least 85% of the doses. Most pharmacists rely on the manufacturer to carry out the quality control testing. A radiopharmacist often does quality control testing daily on many products (Fig. 1-9). Most radiopharmaceuticals are administered intravenously; thus aseptic technique and control of **pyrogens** is of as much concern to the radiopharmacist as it is to the hospital pharmacist who prepares **parenteral** injections (Fig. 1-10).

A radiopharmacist also is much more involved in troubleshooting activities. When the biodistribution of a radioactive tracer is other than expected, it becomes the responsibility of the radiopharmacist to determine the cause of the problem. The biodistribution of the radiopharmaceutical is usually evident. The image obtained in the nuclear clinic provides immediate evidence of the performance of the tracer. Thus, biodistribution is a daily concern of the radiopharmacist.

One area in which radiopharmacy is quite

Fig. 1-13. Radioactive prescriptions are delivered in special vehicles to neighboring hospitals. Special carrying cases are used to assure safe handling of drugs.

similar to other areas of pharmacy is in the clinic. The radiopharmacist is also a clinical pharmacist. He is concerned with drug interactions and with adverse reactions. He is involved with consulting the physicians on the performance of the tracer and in recommending which tracers can be used in concert with other drugs that have been given to the patient. The radiopharmacist consults mostly with physicians and nuclear medical technologists rather than with patients. Most patient contact will involve only the taking of drug histories and the extraction of other data that can influence the biodistribution of the tracer (Fig. 1-11).

A regular pharmacy is basically a one-way street, accepting prescriptions primarily from patients and dispensing most drugs directly to the patient. Only rarely will radiopharmacists dispense directly to a patient. Usually, the drugs are dispensed to nuclear medicine physicians who administer the drugs intravenously to the patient in the nuclear medicine clinic. The syringes, needles, and other injection paraphernalia are radioactive wastes. Usually, these are returned to the radiopharmacy for disposal or storage. Thus, a radiopharmacy is a two-way street. The volume of wastes received may be greater than the volume of materials dispensed.

The greatest area of difference between a radiopharmacy and other pharmacies is the control of radioactive materials and the concern for radiation safety. The control of radioactive materials is basically similar to that of other controlled substances, such as narcotics. The practice of radiation safety is basically similar to the control of microbiologic contamination. Aseptic techniques can thus be readily augmented to include radiation safety techniques (Fig. 1-12).

The regulatory problems of a radiopharmacy are more complex than those of other pharmacies. Essentially, all regulations that apply to pharmacies or pharmacists apply to radiopharmacies and radiopharmacists. Not all state

boards of pharmacy have become involved in radiopharmacy; however, the trend indicates that those currently not involved soon will be. The additional agencies that regulate radiopharmacies are the Nuclear Regulatory Commission (NRC) (or the state equivalent, in agreement states) and the Department of Transportation (DOT). NRC controls the possession and use of radioactive materials; DOT controls the transportation of radioactive materials (Fig. 1-13).

Types of radiopharmacies
HOSPITAL RADIOPHARMACIES

Often a hospital that has a nuclear medicine service will prefer to have its own hospital radiopharmacy located within the department. This radiopharmacy is usually a subdivision of the nuclear medicine clinic. In many cases, the person in charge of the radiopharmacy may have little involvement with the regular hospital pharmacy. In some hospitals the radiopharmacy is under the joint administrative control of both the hospital pharmacy and the nuclear medicine clinic. This has the advantage of keeping the radiopharmacy working directly in nuclear medicine but allowing it to take advantage of personnel available in the hospital pharmacy and to use some of the services and facilities available from the hospital pharmacy. When the hospital radiopharmacy is located in the nuclear medicine clinic, it usually comes under the direct supervision of the nuclear medicine physician or a nuclear medical scientist.

When the hospital radiopharmacy is under the supervision of a resident nuclear medical scientist or nuclear medicine physician, the day-to-day work is usually done on a rotational basis among the nuclear medicine technologists. Thus, it is important that the technologists be trained in the various radiopharmacy techniques.

CENTRAL RADIOPHARMACIES

National radiopharmacies have grown up in several countries. One example is Australia, where a national radiopharmacy synthesizes or imports radionuclides, manufactures reagent kits for use throughout the country, and supervises the quality control of radiopharmaceuti-

cals. The laboratory also carries on a vigorous research and development program. The National Radiopharmacy of Denmark is more involved in the control and performance of radiopharmaceuticals than it is in the actual manufacturing of drugs. National radiopharmacies provide a central focus for the control, introduction, and development of radiopharmaceuticals within the country. The national radiopharmacies have also played a very important role in providing input into the International Atomic Energy Agency for the development of recommendations and quality control procedures.

In the United States there are several university radiopharmacies that supply radiopharmaceuticals to a region, often to an entire state. These university or statewide radiopharmacies provide training laboratories for students of radiopharmacy, as well as central depots for the elution of ^{99m}Tc from large generator systems and for the preparation of unit doses of radiopharmaceuticals that can be distributed on prescription to physicians and hospitals throughout the territory serviced (Fig. 1-14). The advantage of this type of operation is that the cost can be reduced by greater and more rapid use of the inventory of radiopharmaceuticals. The faster radiopharmaceuticals are used, the less radioactive tracer is lost by radioactive decay.

Commercial radiopharmacies are currently being developed across the United States. These radiopharmacies are usually managed by a licensed pharmacist who must also obtain authority from state or national regulatory agencies to handle radioactive materials. These central radiopharmacies can provide the same economic advantages to the individual physician as the state or university operations. Central radiopharmacies and commercial radiopharmacies can provide a large number of small hospitals with radiopharmaceuticals more economically than the clinic can purchase the drugs directly. In this manner, one radiopharmacist can serve a dozen or more nuclear medical clinics.

Training of radiopharmacists

It is only in the last few years that the training of radiopharmacists has become formal-
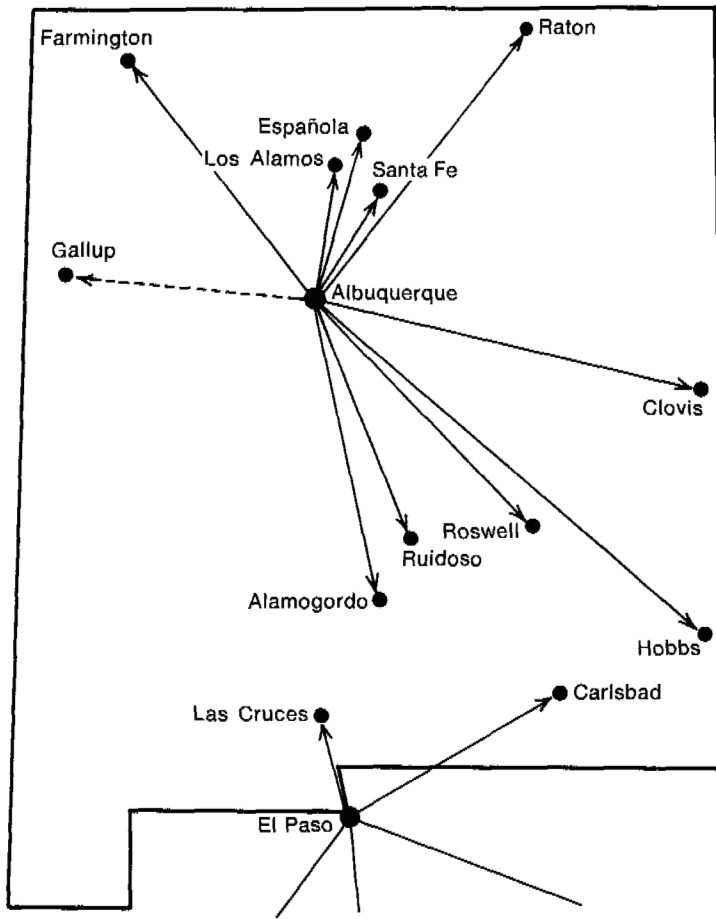
Fig. 1-14. Map of New Mexico showing distribution of radiopharmaceuticals throughout state from two nuclear pharmacies, one located in Albuquerque, and the other in El Paso, Texas. Central radiopharmacies that service multiple nuclear medicine clinics are called *nuclear pharmacies*.

ized. Survey courses are currently being introduced into most undergraduate programs in colleges of pharmacies. Undergraduate specialization in radiopharmacy is available in a few colleges of pharmacy. Short courses and extended training periods or residencies in radiopharmacy are also available at a few colleges. Graduate credit courses and programs are being introduced in several colleges of pharmacy.

To prepare oneself to go into the field of radiopharmacy, a bachelor of science degree in pharmacy or certification as a nuclear medicine technologist is a good beginning. This can be followed by a year of specialized training in radiopharmacy that includes the safe handling of radioactive materials, principles of tracer techniques and nuclear medicine, radiochemis-

try and analytical chemistry, dispensing radiopharmacy, and clinical radiopharmacy. Courses in hospital pharmacy and in sterile techniques are also of importance to the person who wants to practice radiopharmacy. It takes about a year of additional training beyond the 4 years of college to prepare oneself for the routine work of both dispensing and clinical radiopharmacy. This can be accomplished by on-the-job training; however, participation in a year-long residency program or the completion of a master's or doctoral program in radiopharmacy is preferred.

Suggested readings

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Tracer techniques in medicine

Tracer techniques: uses and advantages

What do we mean when we talk of a tracer? What is the tracer technique? One of the oldest tracer techniques is to put a colored cork in a river and watch the cork move along tracing the river's current. In this situation the cork is not an exact tracer of the current: its properties are different from the water, and it moves at a slightly different rate, since it is affected differently by variables such as wind than are the water molecules themselves. A water-soluble dye is a better tracer than the cork. However, to trace most accurately the current of the river, it is necessary to use actual molecules of water that are going to have exactly the same properties as all the molecules of water in the river. These molecules can be used as true tracers only if they also have some property such as radioactivity that will allow us to distinguish them from the molecules of water that we are tracing.

Several different kinds of tracers can be used that approximate true tracers. The first of these are the dyes. Ink, poured into the water, can be observed as the color traces the current. This technique is actually used to trace water flowing inside caves to determine where the underground stream surfaces. In this example, the human eye is the detector. There are, however, more sensitive optical detectors than the human eye. These detectors are *spectrometers*. The use of spectrometry expands the range of dyes that can be used. In addition to dyes that can be seen in the visible spectrum, dyes which emit in the ultraviolet or the infrared region of the spectrum can also be employed. Both **qualitative** and **quantitative** studies can be done

using these methods. For instance, the presence of dye in the river water indicates where the spring from inside the cave flows into the river. The actual concentration of the dye is a quantitative indicator of how much dilution has occurred in the water as it went from the cave into the main surface water supply.

Isotopes are the truest of the tracers. The The term *isotope* is used to denote an atom of a different mass of the same element. For example, iodine 129 is an isotope of iodine and differs in mass by 2 from the most common isotope of iodine, iodine 127. Chemically, the behavior of the two isotopes are identical except when atomic mass is a reaction parameter. Even in this case, the reaction rates of the 129 isotope chemically approximates that of other atoms of iodine because its mass differs from the mean mass by less than 2%. In general, an isotope is a true tracer except in situations where there is a significant isotope effect. An isotope effect is most frequently observed when using tritium (^{3}H) to trace hydrogen (^{1}H) in reactions where the kinetic rate is a function of the atomic mass of the hydrogen. Practically, the isotope effect is rarely encountered in biologic tracer studies.

When atoms of different mass are used as a tracer, one detector that can be used is the **mass spectrometer.** The actual measurement employed is the mass ratio or changes in mass ratio. In some instances, **nuclear magnetic resonance spectrometry** or **neutron activation analysis** can be used to detect the isotopic tracer.

With so many kinds of tracers available to us, why do we choose to use the radioactive ones? The reason is that analytical methods for detecting radioactivity are among the most sensi-

Fig. 2-1. Patient has just received intravenous dose of ^{99m}Tc sulfur colloid that is being trapped in liver. Nuclear medicine technologist positions patient so that accumulation of radioactive tracer in patient's liver is visualized by Anger camera. Oscilloscope in background displays image of liver.

tive in the world. Most other measuring systems depend on **colligative** properties of the molecules. For example, if we measure something using weight, volume, or intensity of color, we are required to have a large collection of atoms with the same property all in the same place and at the same time in order to elicit the colligative property. With the radioactive method we have the possibility of detecting a single atomic event. Thus, when we are measuring radioactivity, the mass of tracer atoms required to conduct the tracer experiment can be diminishingly small. So small, in fact, that we do not alter the system at all by adding the tracer. The second tremendous advantage of the radioactive tracer method over the other methods is that the detecting device can be placed some distance from the system in which the tracer atoms are being used. The tracers are administered intravenously, and the detector is outside the body (Fig. 2-1). In the jargon of the field, we say that these tracer techniques are *noninvasive.* This allows us to see what is going on inside the body without interfering with the subject's biochemistry, physiology, or anatomy.

The disadvantage of the radioactive tracer technique is that we expose the individual to radiation. Fortunately, the amount of radiation that is given is *not* large enough to produce detrimental biologic consequences in a significant portion of the population under study. However, since the possibility of radiation damage is greater than zero, it is always necessary to design the radioactive tracers so that radiation exposure is minimized while detection sensitivity is maximized. This is accomplished by using isotopes (radionuclides) with radiations energetic enough to permit their detection outside the body. We try to maximize useful radiations and minimize useless or harmful radiations. Radionuclides with a short half-life and with radiation suitable for detection are selected as biologic tracers. The best nuclides emit a single penetrating gamma ray (80 to 400 kev) and little nonpenetrating beta and betalike radiations (Fig. 2-2). Its half-life is just long enough to get the job done. Thus, when we want to trace something for an hour, an isotope with a half-life of an hour or two is superior to one with a half-life of a week or a month. With
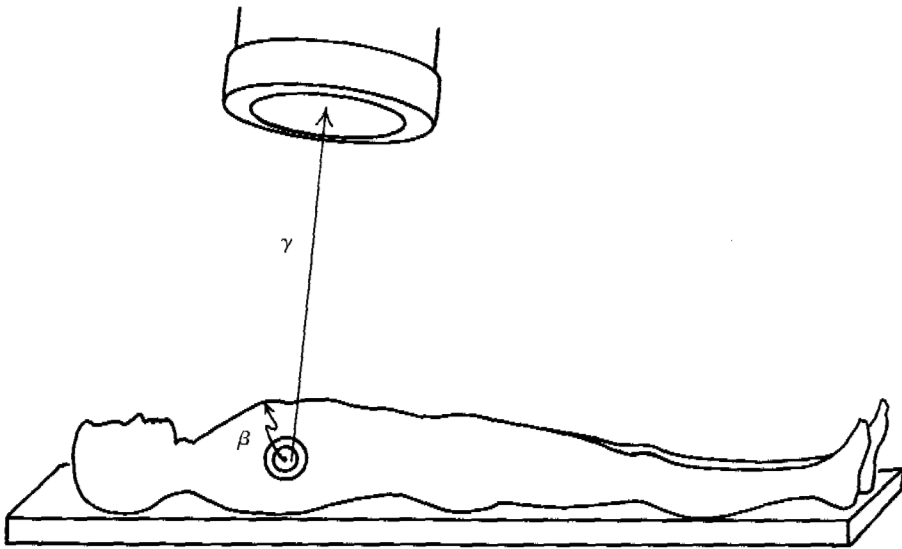
Fig. 2-2. Radioactive element undergoes radioactive decay inside patient. Gamma rays emitted during decay can be detected with Anger camera. Beta and betalike radiations do not emerge from body; they thus irradiate patient without providing usable signals that can be registered or used for imaging.

isotopes of longer half-lives, unnecessary radiation exposure continues after we are finished with our measurements.

Use of tracers to determine mass and space
LAW OF CONSERVATION OF MATTER

The first tracer principle follows from the law of conservation of matter. Simply stated, the amount of radioactivity is not changed by dilution. For instance, if I have 1 mCi of ^{99m}Tc, and I pour this millicurie into the Atlantic Ocean, the Atlantic Ocean now will have 1 mCi of ^{99m}Tc in it. By expressing this concept mathematically, we derive the first and simplest form of the dilution equation. This is expressed in equation 1 and illustrated in Fig. 2-3.

$$A_{before\ dilution} = A_{after\ dilution} \quad \textbf{(1)}$$

where A is used to denote radioactivity

The total amount of radioactivity, A, is equal to the activity per unit volume, that is, the concentration, C, times the volume, V.

$$A = VC\ (or\ V = A/C) \quad \textbf{(2)}$$

where A = total radioactivity, usually in units of μCi

V = volume, usually in units of milliliters (ml)

C = concentration, usually in units of $\mu Ci/ml$

Since by our first principle, this statement (equation 2) is true both before and after dilution, we are allowed to write the third equation:

$$(V \times C)_{before\ dilution} = (V \times C)_{after\ dilution} \quad \textbf{(3)}$$

You may notice that this is the same equation used for calculating the dilutions of regular chemical solutions, which is shown here:

$$(ml \times N)_{before\ dilution} = (ml \times N)_{after\ dilution} \quad \textbf{(4)}$$

where N denotes **normality,** the concentration term, and ml is the volume term

Thus, equation 3 is actually equation 4 with radiochemical units substituted for the usual chemical units.

RED CELL MASS

An example in which the principles of isotope dilution are used routinely in nuclear medi-
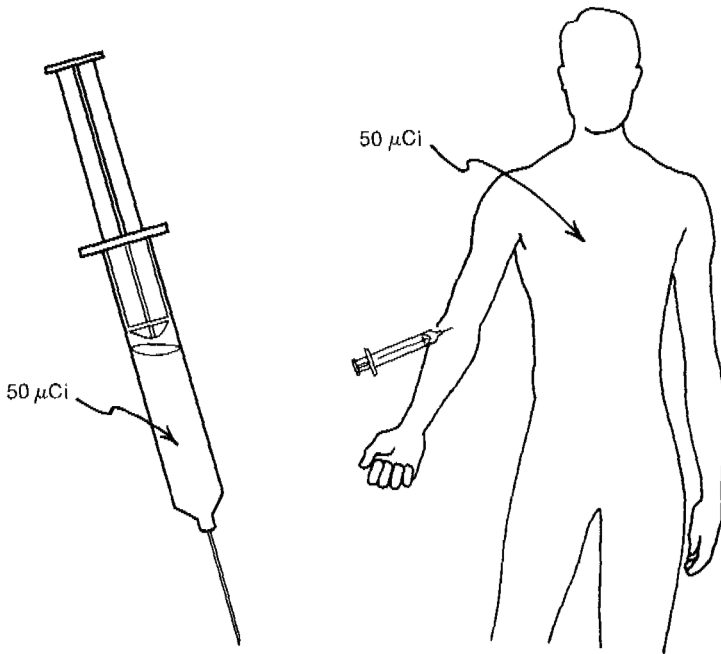
Fig. 2-3. Law of conservation of matter states that total radioactivity is not changed by dilution. Thus, if 50 μCi dose is given to patient, patient contains 50 μCi. Only the concentration of radioactivity is changed. When changes in concentration are measured, volume of distribution can be calculated from equations derived from law of conservation of matter.

cine is to measure a patient's total mass of red blood cells (RBCs). A sample of the patient's blood is collected and incubated with a solution of sodium chromate. The chromium used is the isotope, chromium 51. The radioactive chromate ions diffuse into the red cells, where they are reduced to chromic ions. The chromic ions then bind to structural proteins inside the cell or onto the cell walls or internal membranes. Between 50 and 100 μCi of radiochromium are tagged to the RBCs. An exact volume of the chromium-tagged blood, usually 10 ml, is injected into a peripheral vein of the patient in such a way that complete delivery of the radioactive solution is assured. When the tracer has had time to mix completely and equilibrate with the rest of the patient's blood (15 to 20 minutes after injection), a second sample of blood is withdrawn. A different venipuncture site is used to make sure no cross-contamination occurs. By measuring and comparing the radioactivity in an *aliquot* of the tagged blood (the standard) to an aliquot of the blood of the pa-

tient into which the tracer has been diluted (the unknown), the patient's volume, that is, the volume of dilution, can be established.

The blood volume is calculated using isotope dilution equations derived from the principle of conservation of matter. These equations have to be modified somewhat to account for other factors: (1) the **hematocrit** and (2) the percent of the radioactivity that actually is tagged to the cells. If, after the tagging reaction, the cells are washed three times to remove unbound radiochromium and then administered back to the patient, and if the cells that are collected after dilution are separated from plasma, equation 3 can be used directly. In practice, however, it is easier to carry out the more complicated mathematics and avoid the more time-consuming cell-washing procedures. These mathematical manipulations allow for the correction for the two points just mentioned. Equation 5, which results from the measurements and determinations shown on p. 21, is used to calculate red cell mass.

Measurements	Denotations	
	Standard, value before dilution	**Patient, value after dilution**
cpm/ml, whole blood	A_{WB1}	A_{WB2}
cpm/ml, plasma	A_{P1}	A_{P2}
Hematocrit	Hct_1	Hct_2

Key values	Determination	Denotation
Known	Volume of tagged blood injected	V_1
Unknown	Volume of RBCs in patient	V_{RBC}

Intermediate calculations	
Radioactivity injected in RBCs	$A_{RBC} = V_1 [A_{WB1} - A_{P1} (1 - Hct_1)]$
Concentration of radioactivity in RBCs after dilution	$C_{RBC} = \dfrac{A_{WB2} - A_{P2} (1 - Hct_2)}{Hct_2}$

$$V_{RBC} = \frac{A_{RBC}}{C_{RBC}} = \qquad (5)$$

$$\frac{V_1 [A_{WB1} - A_{P1} (1 - Hct_1)] Hct_2}{A_{WB2} - A_{P2} (1 - Hct_2)}$$

VOLUMES OF DISTRIBUTION

If we administer a small volume of radio-labeled human serum albumin to a patient, follow this by taking a series of serum samples from the patient as a function of time after administration, and measure the concentration of the tracer in the serum, we can plot a curve as shown in Fig. 2-4. The radioactivity decreases in each sequential sample. The decrease is gradual and linear; this permits extrapolation of the curve back to the time of administration (t_0). The extrapolated concentration at t_0 is a function of the initial volume of distribution (V_0). Since the volume of the tracer (the radiopharmaceutical) is so small, its effect on the total serum volume of the patient is nil. Thus, we can rearrange equation 3 to calculate the initial volume of distribution:

$$V_{of\ distribution} = \frac{V_{tracer} \times C_{tracer}}{C_{t_0}} = \frac{A}{C_{t_0}} \qquad (6)$$

where A = total radioactivity injected
C_{t_0} = extrapolated concentration at t_0

Volumes of distribution do not necessarily correspond to well-defined spaces within the body. For example, the hematocrit is not constant throughout the body. This means that, even after uniform mixing of tagged RBCs with the rest of the blood, the concentration of tracer cells is not the same everywhere in the blood pool. The tracer cells are uniformly mixed in the RBC compartment; the RBCs, however, are not uniformly diluted in the whole blood. The volume of distribution is therefore the volume that the tracer would occupy if it were uniformly diluted throughout the compartment into which it was initially injected.

You can see from Fig. 2-4 that the volume of distribution increases with time after administration. Several factors contribute to this. Some of the tracer can leak or be transported into another compartment. Some of the tracer can be metabolized or excreted. Some of the tracer can be chemically degraded. These factors make the extrapolation back to $t = 0$ necessary to get reproducible data.

The absolute radioactivity also decreases with time because of radioactive decay. We usually avoid the complicated calculations needed to correct for decay by counting all
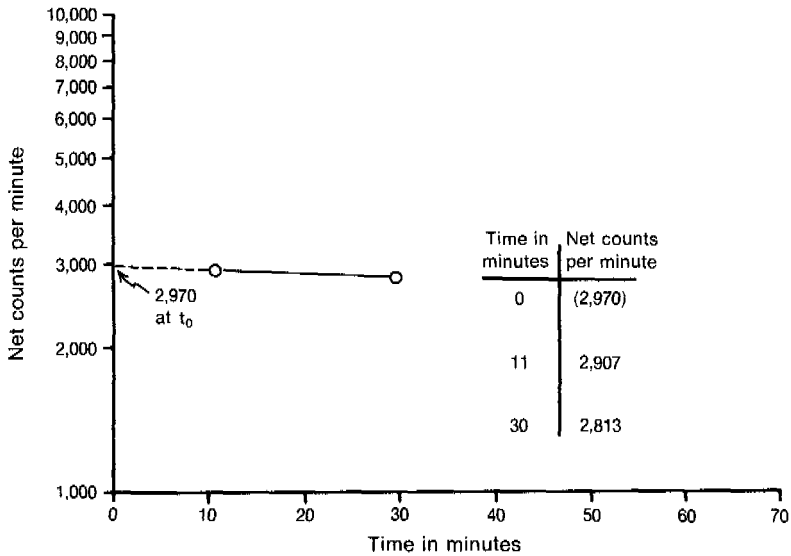
Fig. 2-4. Dose of radiolabeled red blood cells (tagged RBCs) is administered to patient. Concentration of radioactivity in blood is measured 10 and 30 minutes after injection. Data are plotted on graph paper and curve extrapolated back to time of injection (t_0). This allows for calculation of initial volume of distribution.

Table 2-1. Relationships of cpm and μCi to counting efficiencies for the purpose of calculating volumes of dilution

Sample	Counting efficiency cpm/dpm*	μCi $t = 0$	Net cpm $t = 0$	Net cpm $t = 6$	μCi $t = 6$	Arbitrary units of radioactivity
Standard	0.50 (50%)	0.10	111,000	55,500	0.050	1.00
Unknown	0.50 (50%)	0.03	33,300	16,650	0.015	0.33

*dpm is disintegrations per minute. 1 μCi = 2,220,000 dpm.

samples along with the standards at approximately the same time. On a practical basis, we measure concentration in units of cpm/ml (counts per minute per milliliter). Counting efficiency is the ratio of detected cpm/μCi. The data in Table 2-1 illustrate this point. You can notice from these data that both the standard and the unknown radioactivity (either μCi or cpm) are decreasing with time. However, counting efficiency and the ratio of radioactivity between the standard and the unknown are constant with time. Therefore, when the standard and the unknown are measured at approximately the same time, neither efficiency nor decay correction has to be made; that is, the following relationship holds:

$$\mu\text{Ci}_{unk} = \frac{\text{cpm}_{unk}}{\text{cpm}_{std}} \times \mu\text{Ci}_{std} \qquad (7)$$

It is not even necessary to know the true radioactivity of the standard, since the ratio of radioactivity of the standard to that used as a tracer is fixed by the experimenter. For example, if one arbitrary unit of radioactivity is used as a standard and a duplicate amount is used as the tracer, the ratio of cpm of the unknown to the cpm of the standard measures the fraction of the standard that is in the sample. The simplified calculation of the volume of distribution thus becomes

$$V_{of\ distribution} = \frac{\text{cpm}_{1\ ml\ of\ std}}{\text{cpm}_{1\ ml\ of\ unk}} \qquad (8)$$

Table 2-2. Dynamic studies with radioactive tracers

Study	Tracer	Region imaged	Lesions or pathology detected
Cisternography	^{111}In DTPA	Head and neck	Blockage or slowed cerebral spinal fluid flow
Cerebral blood flow	^{99m}Tc DTPA	Head and neck	Blockage of carotid arteries, arteriovenous malformations, or other arterial blood flow abnormalities
Dynamic thyroid	^{123}I$^-$	Throat	Abnormal total or regional thyroidal iodine uptake rates
Nuclear cardio-angiography	^{99m}Tc HSA	Chest	Congenital heart defects, aneurysms, myocardial dyskinesia, cardiomegaly
Dynamic liver	^{99m}Tc SC	Chest and upper abdomen	Detection of hypervascular or hypovascular hepatic lesions and abnormal colloid clearance rates
Cholecystography	^{99m}Tc HIDA	Upper abdomen	Obstructive biliary disease
Gastric emptying	^{113m}In	Upper abdomen	Abnormal gastric emptying rates, gastric regurgitation
Pulmonary ventilation	^{133}Xe	Upper back	Obstructive airways
Renogram	^{131}I Hippuran	Back	Renal dysfunction
Dynamic kidney	^{99m}Tc DTPA	Back	Obstructive renal vascular disease or obstructed urine flow
Cistogram	^{99m}TcO$_4^-$	Lower abdomen	Reflux of urine
Isotope venogram	^{99m}Tc microspheres	Legs	Thrombosis
Adrenal uptake	^{131}I NP 59	Back	Adrenal dysfunction
Rose bengal uptake	^{131}I rose bengal	Upper abdomen	Polygonal cell dysfunction and obstructive biliary disease

when 1 ml of tracer is administered. Often the standard is "too hot to count," that is, it contains so much radioactivity that it is above the linear range of the detector. In such cases, the standard will be diluted, and an aliquot taken for counting. Frequently, 1 ml of radioactivity will be injected into the test subject, 1 ml will be diluted to 1 liter, then a 1 ml aliquot of the diluted standard will be used as the counting standard. In such a case, the equation to be used for the calculation is

$$V_{\text{of distribution}} = \frac{\text{cpm}_{1 \text{ ml diluted std}}}{\text{cpm}_{1 \text{ ml unk}}} \times D \quad \textbf{(9)}$$

where D = the dilution factor, which was 1,000 in the example just cited. If the unknown counted 100 cpm and the standard counted 1,100 cpm, the volume of distribution would be 1,000/100 × 1,000, or 10,000 ml.

The volume of dilution of a tracer is sometimes used directly as a diagnostic indicator. An example of this is its use in the management of patients with suspected electrolyte imbalances. Usually, simple ionic tracers such as radiopotassium, sodium, halide, or tritiated water serve as the radiopharmaceutical.

Use of tracers to determine rates and pathways

Tracers are used to evaluate the dynamics of physiology and biochemistry. Even the most static structures of living organisms experience turnover. Bone mineral, for example, undergoes continual deposition and reabsorption. The determination of the rates and pathways of dynamic processes relies on the kinetic analysis of tracer studies. Pathology can often be detected from altered absorption, excretion, storage, or turnover rates of vital substances. The study of the rates and pathways of movement of foodstuffs, urine, blood, lymph, air, and spinal fluids forms the basis for such important diagnostic tests as nuclear cardioangiography,

isotopic lymphangiography, and cisternography (Table 2-2 gives a more complete listing).

DYNAMIC STUDIES AND NUCLEAR ANGIOGRAPHY

It has become common practice in nuclear medicine to administer the tracer as a bolus and to take sequential gamma-camera images as the tracer moves from the site of injection through downstream flow channels. Table 2-2 lists several of these diagnostic techniques. You will note as you read through Table 2-2 that both the rates and the pathways are of diagnostic significance in the dynamic imaging procedures. Often the visual images denoted with the time of imaging are sufficiently quantitative to arrive at the diagnosis (Fig. 2-5). Sometimes it becomes helpful to quantitate more precisely the flow or clearance rates; these rates can be displayed as an array of relative intensities that form a map of the function being evaluated. This type of image, which is generated from a computer analysis of a series of images as a function of time, is referred to as a functional image. Fig. 2-6 is such an image.

TRACER CLEARANCE AS A MEASURE OF BLOOD FLOW

A tracer is cleared from the bloodstream at a rate proportional to the blood flow to the organ where clearance occurs and to the efficiency of the clearance mechanism. The liver normally has a greater than 85% efficiency for the removal of radioactive particles from the blood. This is so efficient, in fact, that the rate of clearance of such particles can be used to estimate liver blood flow.

Blood flow can also be studied using washout techniques. A tracer deposited in a tissue is removed by diffusion into the local blood or lymph supply, which washes the tracer away. If the tracer freely diffuses into the capillaries, then the washout rate is totally dependent on the blood flow. This technique, which might be called the *tracer depot method,* has been used to determine local skin or muscle blood flow (Fig. 2-7).

The general equation for calculating blood flow by the blood clearance or the tracer washout technique is
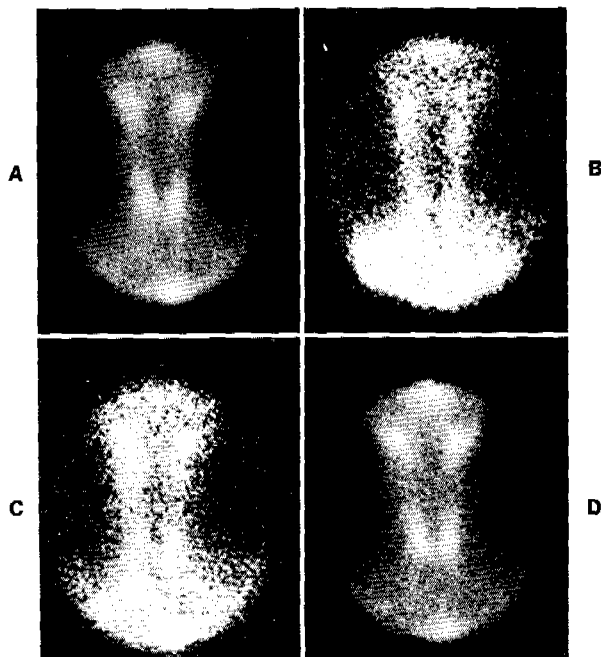
$$A_t = A_0 e^{-kt} \tag{10}$$

Fig. 2-5. Sequential Anger-camera images of neck after injection of sodium pertechnetate (^{99m}Tc). Notice that carotid arteries are seen in initial images and that thyroid and parotid glands are visualized by 1 minute.
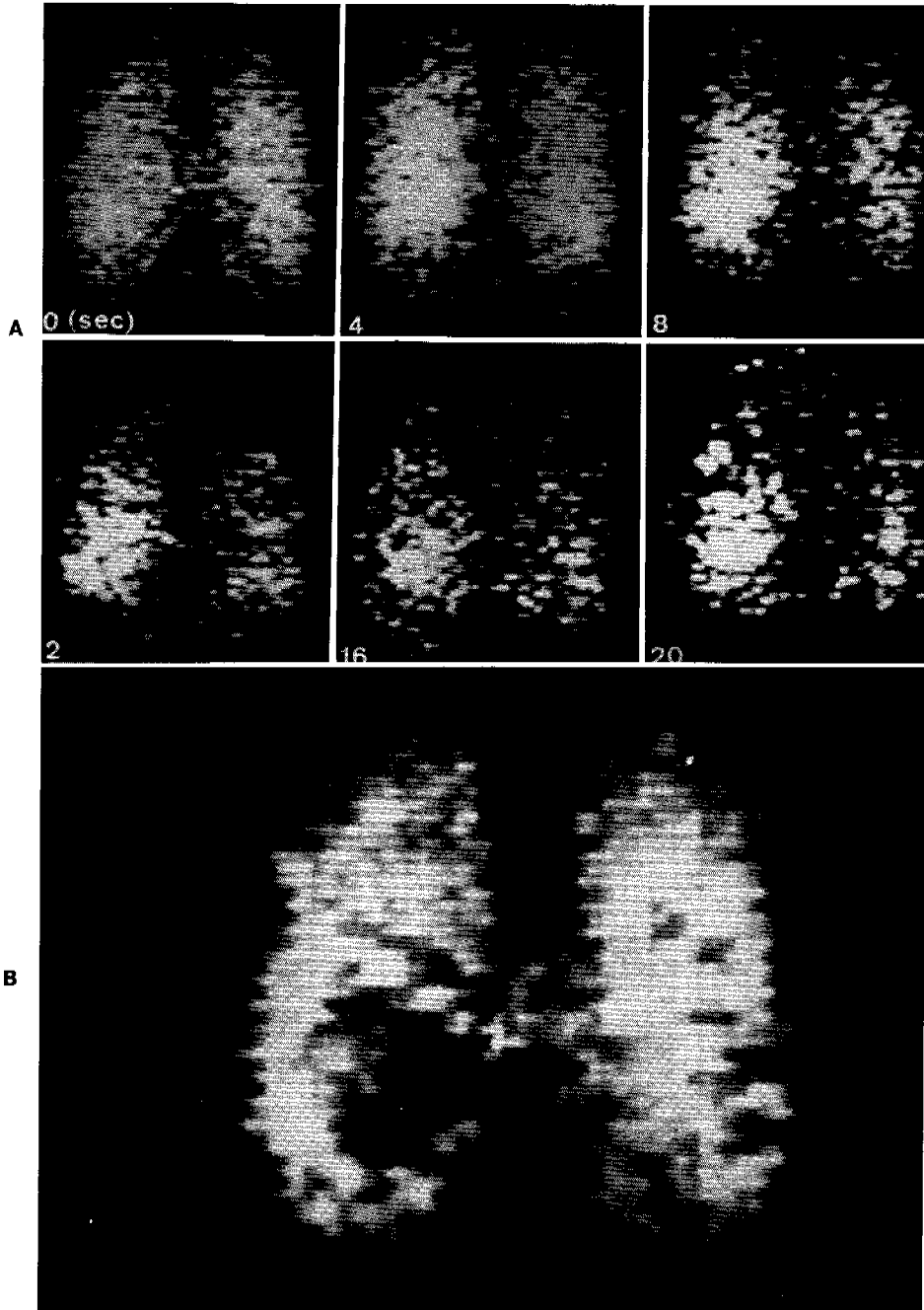
Fig. 2-6. A, Sequential images of patient's chest after having lungs ventilated by xenon 133. Areas of lungs with poor ventilation due to chronic obstructive lung disease such as emphysema are slow at "washing out," that is, clearing radioactive tracer gas. **B,** Functional image composed of regional washout constants calculated from data used to make up images shown in **A.** (From Strauss, H. W., Pitt, B., and James, A. E.: Cardiovascular nuclear medicine, St. Louis, 1974, The C. V. Mosby Co.)
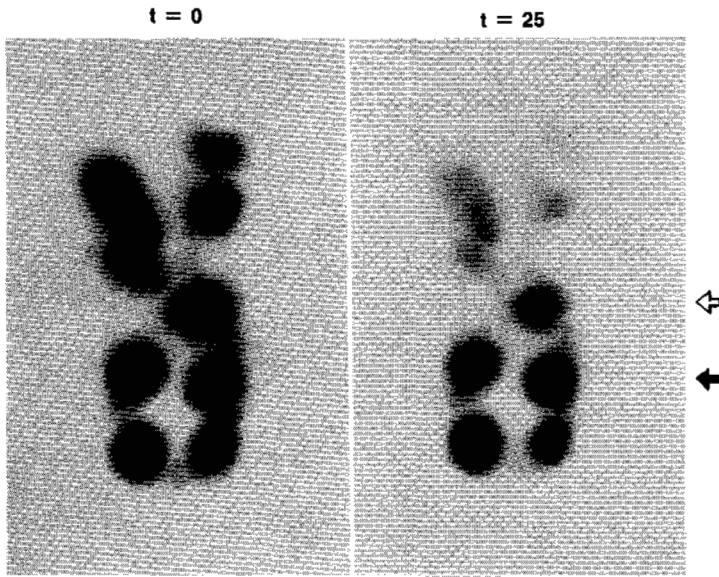
Fig. 2-7. Gamma scintigram of ten intradermal injections of microdroplets of Na $^{99m}TcO_4^-$ in skin flap on back of pig. Pictures were taken at time of injection and 25 minutes after injection. Upper part of graft (above open arrow) is viable, and lower part of graft (below solid arrow) is dead. When there is skin blood flow (i.e., viable tissue), tracer is washed out (clearance constant was 0.026 min^{-1}). When there is no flow because tissue has died, tracer does not wash out (clearance constant was 0.002 min^{-1}). (From Munderloh, S. H., Damron, J. R., Orgel, M., and Knight, R. L.: Predicting skin flap survival by radioisotope washout. Unpublished.)

where A_t = the radioactivity at any time, t, in such units as cpm
A_0 = the initial radioactivity in the same units
k = the clearance constant, in units of minutes^{-1}, for example
t = time in units such as minutes

In cases where a single organ is responsible for clearance, then the uptake rate and the blood clearance rates are identical. Thus, the rate of accumulation of ^{99m}Tc HIDA can be measured over the liver, or the rate of ^{99m}Tc HIDA clearance over the head (cerebral) blood pool can be measured. The rates should be identical. These rates are determined using the same mathematical techniques that we use to determine radioactive decay rates. Fig. 2-8 demonstrates clearance and uptake curves. When the data are plotted on semilog paper, as shown in the lower parts of the figure, a straight-line relationship occurs. The rate constant is directly obtained as the slope of the line. If the data do not fall on a straight line, then more complex kinetics

are suggested, and the student is referred to more comprehensive texts such as Sheppard's.*

The clearance constant, k, is the fraction of the tracer removed per unit of time. If the blood volume is also determined, the actual clearance can be estimated:

$$Clearance = k \times blood\,volume \qquad (11)$$

Relative clearance is sufficient for some applications. To give percentage cleared per unit of time, k is multiplied by 100.

INDICATOR CONCENTRATIONS AND TRANSITS AS MEASURES OF BLOOD FLOW

Blood flow can also be determined from measurements of indicator concentrations over time downstream from a bolus injection. Alternatively, **mean transit times** can be measured. The mean time is equal to volume divided by flow. The student is referred to basic tracer text-

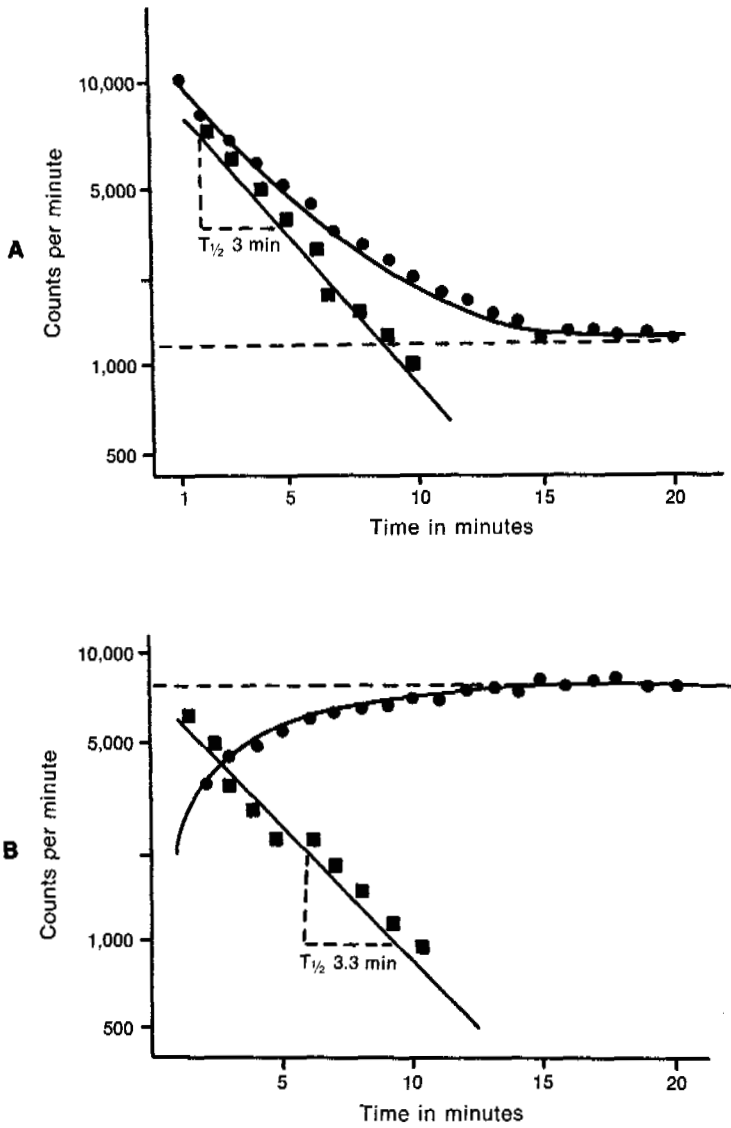*Sheppard, C. W.: Basic principles of the tracer method, New York, 1962, John Wiley & Sons, Inc.

Fig. 2-8. A, Clearance of radioactive tracer from blood measured with detector focused at temple (to measure radioactivity in cerebral blood pool). **B,** Uptake of same tracer by liver.

books for a complete development of these tracer concepts.

ABSORPTION, METABOLISM, AND TURNOVER STUDIES

Radioactive tracers often provide the simplest, the most accurate, and the most sensitive means for measuring absorption, **metabolism,** or turnover of substances. Diagnosis can often be made from measurements which reveal that these rates are altered. Some of the more important diagnostic tracer tests are listed in Table 2-3.

Use of tracers in quantitative microanalysis

In the previous section, we discussed the methods of tracer kinetics. Alternatively, tracer statistics are also diagnostically useful. From tracer statistics come a large group of methods for the analytical determination of minute amounts of important biologic substances in

Table 2-3. Nonimaging, in vivo tracer kinetic studies

Study	Tracer	Samples	Defects detected
Gastrointestinal protein loss	^{51}Cr albumin	Feces	Gastrointestinal protein enteropathy
Gastrointestinal blood loss	^{51}Cr RBCs	Feces	Gastrointestinal bleeding
Red cell survival	^{51}Cr RBCs	Blood	Anemias
Iron turnover	^{59}Fe^{+3}	Whole body	Abnormal ferrokinetics
Vitamin B$_{12}$ absorption (Schilling test)	^{57}Co B$_{12}$	Urine	Pernicious anemia
^{14}CO$_2$ breath test	^{14}C glucose	Breath	Glucose intolerance
Radioiodine uptake	^{123}I$^-$	Urine or external count over thyroid	Abnormal thyroidal iodine uptake rates (hypothyroid or hyperthyroid function)
Renogram	^{123}I Hippuran	External counting over kidneys	Renal disease
Ocular ^{32}P uptake	^{32}PO$_4^{-3}$	External counting over eyes	Melanoma
Fat absorption studies	^{131}I triolein	Feces	Malabsorption of fats
Protein absorption studies	^{131}I albumin	Feces	Malabsorption of proteins
Platelet	^{51}Cr platelets	Blood	Abnormal platelet loss
Splenic sequestration	^{51}Cr RBCs	External counting over spleen	Hypersplenism
^{125}I-fibrinogen uptake	^{125}I fibrinogen	External counting over legs	Fibrin deposition (thrombosis in legs)
^{131}I-fibrinogen uptake	^{131}I fibrinogen	External counting over kidneys	Fibrin deposition (kidney rejection)

small samples. Here the tracer method is used as a substitute for chemical methods of analysis.

ISOTOPE DILUTION ANALYSIS

The basic principle of isotope dilution was developed on pp. 19 to 23. The same concepts used to measure red cell mass or plasma volume can be used to make quantitative determinations of chemicals. In the examples of red cell mass and plasma volume, the key measurement was concentration of radioactivity. In the use of isotope dilution to measure amounts of chemical substance, the key measurement is specific activity, that is, radioactivity per unit of mass, such as μCi/gram. The basic equation is the same as equation 2, except weight, W, is substituted for volume, and specific activity, S, is substituted for concentration:

$$A = WS \text{ (or } W = A/S) \tag{12}$$

Often in this determination, the weight of the added tracer cannot be ignored as in the previous examples. Again, according to the law of conservation of matter, the amount of radioactivity before and after adding the tracer is constant. Thus:

$$A = (W \times S)_{\text{before dilution}} = \tag{13}$$
$$(W \times S)_{\text{after dilution}} = (W_0 + W_x)S_x$$

where W_0 = the weight of the tracer
W_x = the weight of the unknown
S_0 = the specific activity before dilution, that is, of the tracer
S_x = the specific activity after dilution, that is, of the sample with tracer added

If we solve for the weight of the unknown, equation 14 is obtained.

$$W_x = W_0 (S_0/S_x - 1) \tag{14}$$

These equations are consistent with the derivations of Tölgyessy and Varga, who explained several illustrative examples from the biologic literature and who also derived many other equations that are used in calculations of the many variations on this basic principle. These include reverse isotope dilution, double isotope dilution, and derivative dilution. In addition to the advantage of great sensitivity, these meth-
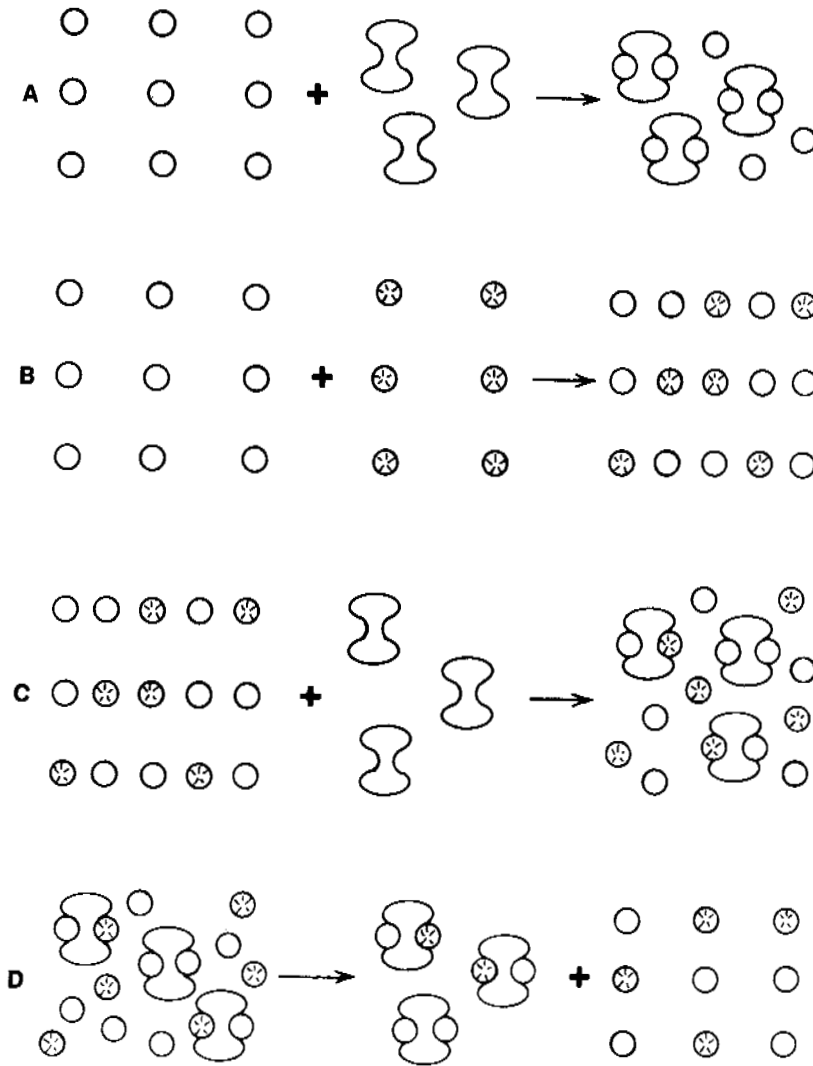
Fig. 2-9. A, Antigen and antibodies combine, with antibodies being limiting or substoichiometric reagent. **B,** Radiolabeled antigen is mixed with or used to dilute original antigen. **C,** After dilution, substoichiometric reagent removes same amount of antigen. **D,** After reaction with antigen, mixture is separated so amount of radioactivity bound to antigen can be measured.

ods often allow for analysis of substances that cannot be achieved by other means. Often a tracer can be used to measure yields from inefficient separation techniques. For example, the determination of thyroxine in the plasma of a rat on a low-iodine diet was achieved by first adding ^{131}I-labeled thyroid hormone to the plasma, then separating the iodoamino acids by extraction and double-paper chromatographic procedures. The final thyroxine preparation was highly purified and free from other iodoamino acids; however, significant and unavoidable losses had occurred during the multiple separations. The recovery of the ^{131}I was then used to measure the overall yield of the separation procedures and to correct the final analytical result to give the total thyroxine in the original sample.

SUBSTOICHIOMETRIC ANALYSIS

Stoichiometry is the part of chemistry which deals with the relative amounts of substances

that combine in a chemical reaction. One **mole** of hydrogen ions combines, stoichiometrically, with one mole of hydroxyl ions to yield one mole of water. If one reagent is in limited supply relative to the other, then the reagent in limited supply (i.e., the substoichiometric reagent) will determine how much reaction product is formed. Thus, if only 0.5 mole of hydrogen ions was available in the preceding example, then only 0.5 mole of water could be produced. Substoichiometric analysis takes advantage of using one reagent as the limiting, or substoichiometric, reagent to divide the radioactive tracer into two chemical species, one combined and one uncombined. As such, the two forms of the tracer can be separated from each other by some simple chemical procedure. The ratio of combined to uncombined radioactivity is measured. This measurement is used as an indicator of the amount of the substance that we want to determine. The amount of thyroid hormone in a small sample of serum is easily determined by this method. Some ^{131}I-labeled thyroid hormone is added to the serum, then all the thyroid hormone, both native and the added tracer, is extracted and reacted with a substoichiometric amount of thyroid hormone antibody. The reaction product, antibody-bound thyroxine, is limited, so not all the tracer becomes bound. The antibody-bound hormone is separated from the unbound hormone by one of several available techniques. One way is to absorb the unreacted hormone onto activated charcoal. Thus, the radioactivity on the charcoal is measured relative to that which remains in solution (i.e., the bound). The more native hormone in the original sample, the more native (nonradioactive) hormone combines with the substoichiometric reagent, and the less radioactivity combines with the antibodies. The amount of hormone in
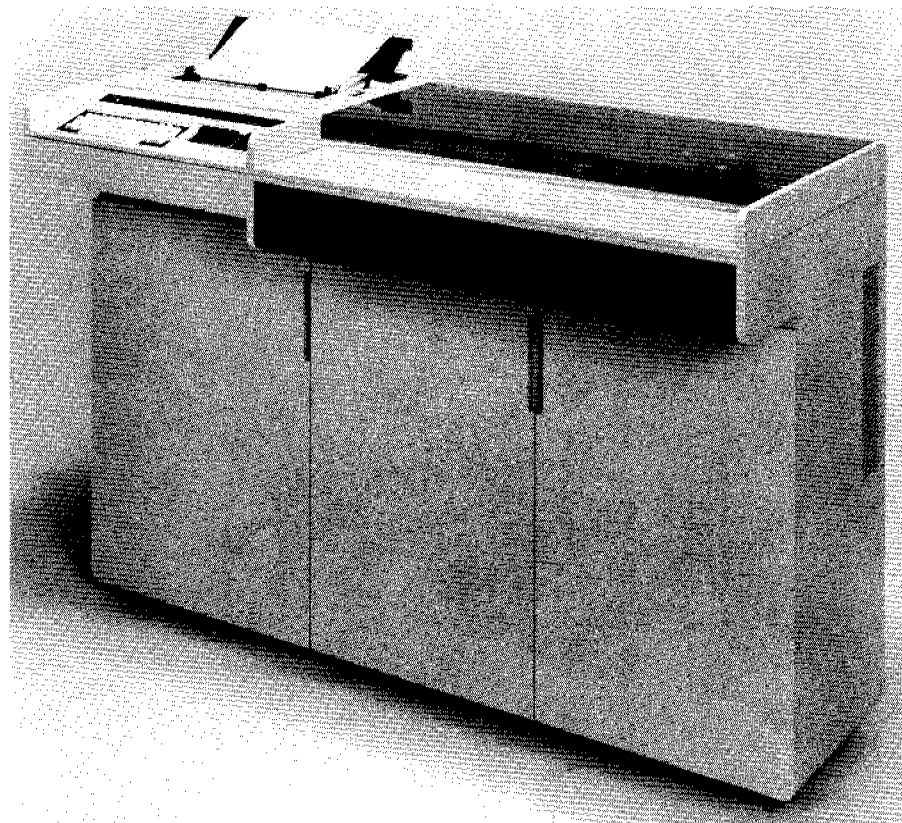
Fig. 2-10. Automatic sample processing scintillation detector equipped with dedicated computer for automated RIA. This is Squibb Gamma Flo^R system introduced in 1977.

the original sample is therefore inversely related to the amount of radioactivity on the charcoal and directly related to the amount of radioactivity that remains in solution (Fig. 2-9). Many variations on this concept have been developed for the measurement of thyroid hormone levels in serum. A variety of reagent kits can be purchased commercially that permit this type of microanalysis to be readily performed in clinical laboratories (Fig. 2-10).

Radioimmunoassay (RIA) is the major type of substoichiometric analysis used clinically because the sensitivity and specificity of the antigen-antibody reaction is so great. Antibodies to many biologically active molecules can be produced using immunologic techniques. Often the substoichiometric reagent is an unpurified antiserum from a rabbit, goat, or other laboratory animal. One animal can produce enough reagent for thousands upon thousands of microanalytical tests.

Competitive protein binding is a somewhat more general term that includes RIA as well as other specific protein-binding reactions. Intrin-

sic factor is a protein that reacts specifically with vitamin B_{12} and thus is used as a substoichiometric reagent in the B_{12} assay. Thyroid-binding globulin can be used as a reagent for the thyroid hormone assay; conversely, thyroid hormone can be used as a reagent for determining serum levels of thyroid-binding globulin. Another general term seen in the literature is radioligand assay. The radioligand would be ^{131}I thyroxine or ^{57}Co B_{12} in the examples just given.

ISOTOPIC EQUILIBRIUM ANALYSIS

If a biologic system, like a living rat, is fed only iodine that comes from a source of uniformly labeled iodine, the specific activity of the iodine in the rat will approach, in time, that of the iodine source (Fig. 2-11). When equilibrium is reached, the specific activity becomes known as it was originally determined by the experimenter. At this time, a measure of radioactivity becomes a direct measure of the amount of iodine in the rat or in tissue samples obtained from the rat. If the rat contains 1 μCi of ^{125}I of
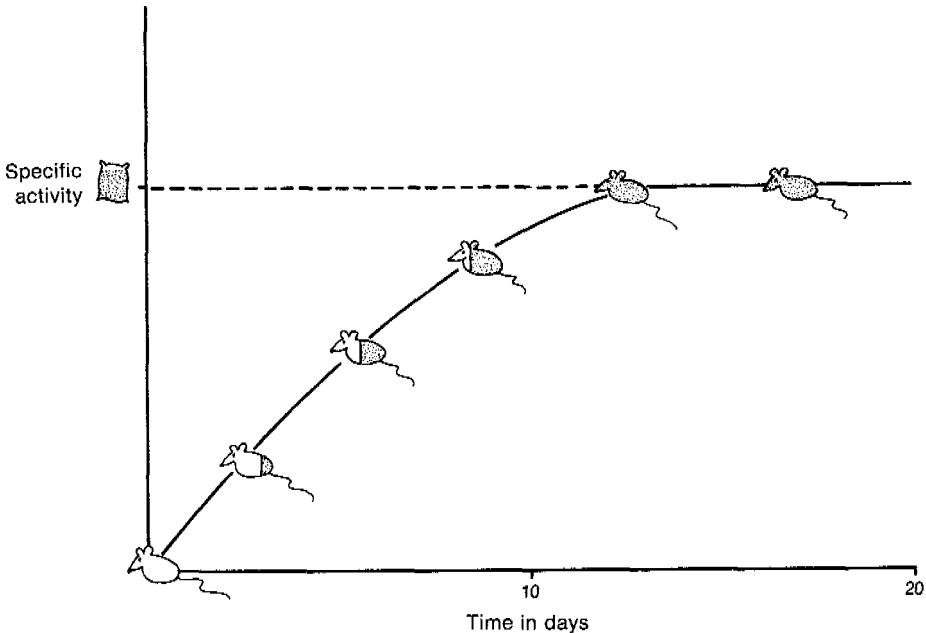
Fig. 2-11. Isotopic equilibrium is achieved when specific activity of test subject is same as that of diet or environment. At isotopic eqilibrium, measurement of radioactivity can be used to determine mass.
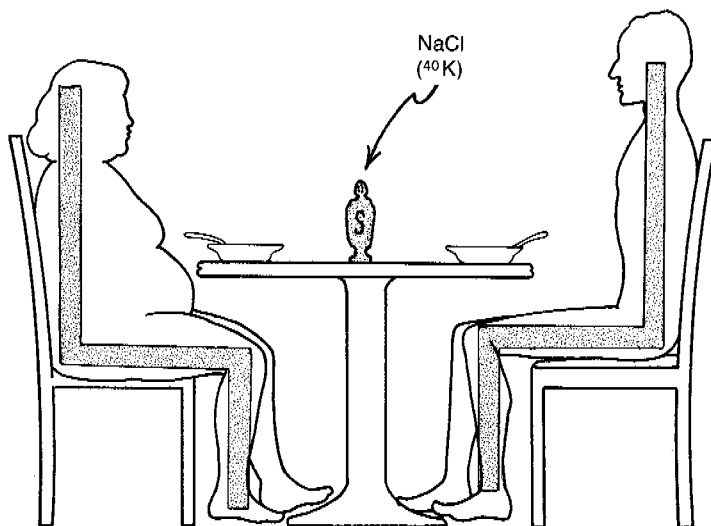
Fig. 2-12. Specific activity of potassium in human body is same as that of environment or diet. Since potassium is primarily associated with muscle tissues, a measure of total-body ^{40}K can be used as indicator of lean body mass. In this drawing, both individuals have same lean body mass *(shaded area)* and thus about same amount of ^{40}K, even though total body mass is greatly different. This is an example of how principles of isotopic equilibrium can be used to determine mass for medically useful purpose.

specific activity of 0.1 $\mu Ci/\mu g$, then the rat contains a total of 10 μg of iodine.

A clinical test that employs this principle is the total body potassium measurement. A whole-body count determines ^{40}K in the subject. The specific activity of potassium in the body is the same as that in the environment; it is 0.0118%. Once the μCi of ^{40}K in the body is measured, total body potassium is determined. The total body potassium is related to lean body mass, so it is used to estimate ratios of lean to fatty tissues (Fig. 2-12).

ACTIVATION ANALYSIS

Nonradioisotopic tracers, that is, enrichments of stable isotopes, can be employed in the tests just described. The radioactivity is induced in the final stage of the analysis by placing the sample in a beam or field of nuclear particles. The nuclear particles activate the tracer isotope, permitting its quantitation by measuring its radioactivity. This method offers the advantage of extreme sensitivity of the radioisotopic tracer method without the necessity of administering a radionuclide to the subject.

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Mechanisms of localization

The magic bullet approach versus the tracer concept

For many years in medicine there has existed the concept that a particular medicine should be used to cure or alleviate a particular condition. We call this the *magic bullet approach.* This idea was prevalent in folk medicine and has persisted to the present. As medicine becomes more scientific and particular organisms are associated with particular diseases, the idea has gained yet more credence. This approach to therapeutic medicine leads to a similar approach to diagnostic medicine, that is, a specific test and a specific answer for each disease and each organ. Each of us can think of appropriate counterexamples, such as the use of penicillin to treat a number of diseases. This is not really a counterexample, since we know of many diseases for which penicillin is not useful at all. X-ray contrast media are indeed useful under several different circumstances, but one does take care to give IVP (intravenous pyelogram) dyes for renal studies and gallbladder dyes for cholecystograms. The magic bullet approach makes use of a specific mechanistic connection between a drug and a disease or organ.

In direct contrast to this approach is the use of the tracer concept as described in the previous chapter. George de Hevesey, one of the fathers of nuclear medicine, applied radioactive tracer methods to the study of chemical and biologic systems. In using tracer methodology it is imperative that we use an infinitesimally small amount of labeled material, that is, that we use high specific activities or materials containing little or none of the nonradioactive form. This is necessary in order to perform physiologic studies without altering the system.

The quantities used must be chosen by reference to the system under study and to the amount of the nonlabeled material already present. The use of tracer techniques implies a certain amount of knowledge about the system, since one cannot very successfully incorporate tracer techniques into the shotgun method of research. Tracer techniques seek to discover normal and abnormal pathways for the movement of a particular material in a particular system and to relate these pathways to disease states whenever possible.

The first nuclear medicine studies capitalized on application of the tracer technique to solve diagnostic questions. Soon, however, the emphasis switched to the magic bullet approach. This is illustrated by the history of the tracer diagnosis of thyroid disease. The first methods for evaluating the thyroid relied on hand-held collimated radiation detectors to measure the uptake of a tracer dose of radioiodine. It was soon appreciated that more information could be obtained by measuring and recording the spatial distribution of the tracer. For instance, clinicians could determine if the nodule felt on the gland had a greater or lesser affinity for the radioiodine than the surrounding tissues. Thus, some physicians began to record thyroidal uptake values on maps they drew to represent the gland. Cassen appreciated the value of such spatially correlated data but did not like to spend so much of his time getting the data. He solved the problem by inventing the rectilinear scanner (Fig. 3-1). This is a collimated scintillation probe that moves back and forth over the area of interest automatically recording the count rate data as a map of the distribution of the accumulated radioactivity.
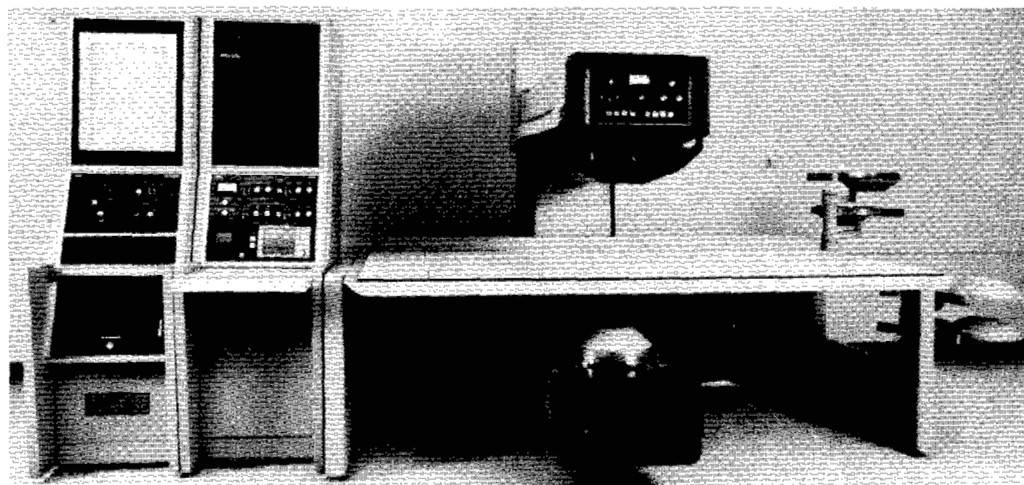
Fig. 3-1. Dual-head rectilinear scanner. *Patient is positioned between two detector heads.* Two rectilinear scans are made simultaneously. (From Rhodes, B. A., editor: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.; courtesy Elscint, Inc.)

This type of nuclear medical technique greatly appealed to radiologists because it provided a way of making pictures of organs they had not been previously able to visualize with other methods. The magic bullet approach became dominant during this next period of the history of nuclear medicine. It began with an extensive search for specific tracers and specific mechanisms that would provide means for localizing radioactivity in organs that clinicians wanted to visualize. Clinicians, accustomed to the diagnostic value of x-ray images, readily appreciated the importance of this new type of image. Radioisotope imaging was rapidly expanded to include visualization of lungs, liver, spleen, heart, kidneys, and brain.

The first radioisotope imaging devices were incapable of viewing more than one point at a time. Thus, tracers were sought that would rapidly accumulate in or around the areas of clinical interest and stay there while the rectilinear scans of these areas were being made. With this approach nuclear medicine, like diagnostic radiology, primarily provided anatomic data to the diagnostician. With the development of radioisotope imaging devices like the Anger camera (Fig. 3-2), which is capable of viewing an extended area of interest repeatedly in time,

a reemphasis of the tracer principles in nuclear diagnosis began. For example, ^{99m}Tc DTPA is no magic bullet for the kidneys, yet it is very useful for visualizing the movement of a substance into and out of the kidneys. Our nuclear medicine procedures are now capable of providing a blend of anatomic and physiologic data.

Thus, as we trace the development of in vivo tracer studies of the thyroid, we see the role of both concepts in the development of the methodology. Early thyroid studies, as well as our current techniques, really stem from both ideas. Radioactive iodine is administered to the patient by mouth. The thyroid is counted at 6 and 24 hours, following the idea for determining the function of the thyroid by use of the tracer concept. However, the iodine concentration after 24 hours remains quite stable and can be used to make a picture of the thyroid, following the magic bullet approach for thyroid scanning. The best of nuclear medicine really does combine the two ideas, allowing us to simultaneously picture the function and anatomy of the gland. Both can then be compared both to normal pictures and to normal functional data to provide more diagnostic data than either approach alone provides.
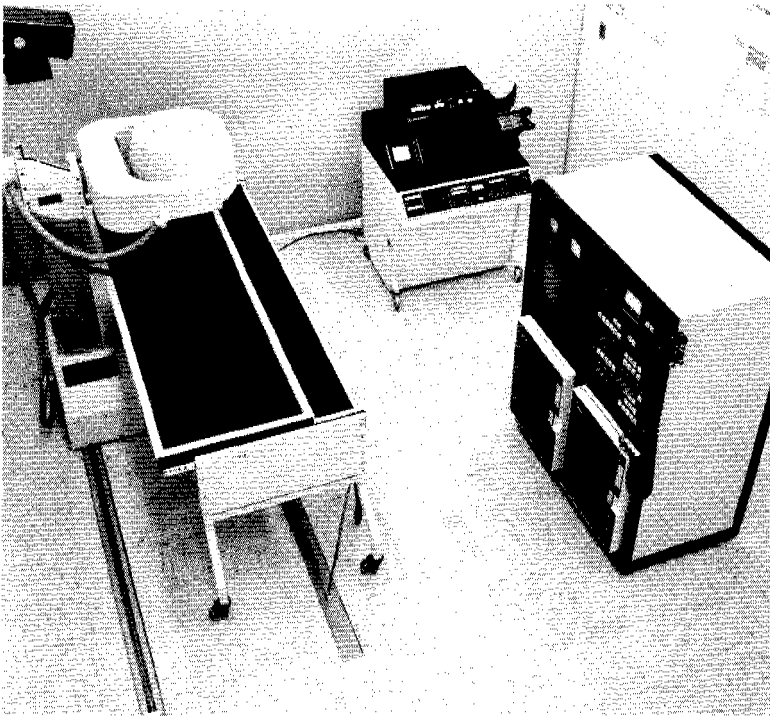
Fig. 3-2. Scintillation camera with whole-body imaging table. (From Early, P. J., Razzak, M. A., and Sodee, D. B.: Textbook of nuclear medicine technology, ed. 2, St. Louis, 1975, The C. V. Mosby Co.; courtesy Ohio Nuclear, Inc.)

In consideration of the mechanisms used for localization of radioactive materials, this chapter will follow a scheme proposed by Wagner some years ago. These mechanisms, however, will be considered from both viewpoints just discussed.

The term *mechanisms of localization* is used to describe the various ways in which radioactive materials are concentrated in specific regions of the body. This differential concentration allows us to study the function of the particular tissue or organ in which the concentration occurs. To outsiders, nuclear medicine must appear to be a trick. The patient sees the technologist inject something into his arm and then aim an instrument at a particular area of the body. All the material seems to come out of identical bottles. On successive days, a single patient may have liver, brain, and bone scans, all obtained after a dose of ^{99m}Tc was injected. The studies thus appear extremely similar; it may even occur to the patient to wonder why

all the examinations were not performed at the same time. The reason, of course, is that different ^{99m}Tc tracers are given for different organ scans and that the radioactivity of one organ often interferes with the study of another organ. It is the carrier substance that determines the biodistribution of a given radionuclide. Thus, by tagging a tracer nuclide like ^{99m}Tc to an appropriate carrier, it can be directed to one of several specific target organs.

Capillary blockage

Capillaries are the small blood vessels, up to about 7 microns (μ) in size, that are the connection between the arterial and venous blood supplies. In the capillaries, the membranes allow transfer of materials in both directions: from the blood to the tissue, as for nourishing the cells, and from the tissue to the blood to remove waste materials. In the lungs, the capillaries allow the blood to come within a membrane of the air we breathe so that oxygen and

other things in the air can be transferred into the blood, and CO_2 and other gases may be passed into the gaseous phase and eliminated. The lung capillaries separate returning venous blood of the right heart circulation from the oxygenated arterial blood of the left heart circulation. Lung capillaries thus are a filter between the venous and the arterial blood supplies.

In order to study the relative regional perfusion of blood to a particular area and to obtain a picture that will represent average rather than instantaneous perfusion, as is shown by the transit of a bit of contrast agent or a bolus of radioactivity, a few of the many capillaries in that area can be plugged or embolized with a radioactive plug. The microembolization occurs in proportion to the location and the amount of the blood flow. To do this, radioactive particles larger than the capillaries (10 to 90 μ) are injected so that the direction of blood flow will take them to the capillary bed whose blood flow is under study. The injection technique must also provide for uniform mixing of the particles with the blood that will be perfusing the region of interest.

The injected particles will plug a small number of capillaries. Only about one in 10^5 capillaries in the lungs is plugged; thus, the pulmonary circulation is not compromised. So that this embolization will not be permanent, the particles are made of biodegradable materials. Human serum albumin (HSA) is often used as the starting material for preparing the radiolabeled particles. The albumin is either **macroaggregated** or made into **microspheres.** The body can phagocytize these particles and remove them from the capillary beds. The HSA must be converted into particles of the required size, either by cooking it into feathery particles called macroaggregated albumin (MAA) or by forming it into spherical balls and cooking the balls, called microspheres. The balls can be sorted quite accurately for the correct size.

Besides albumin, either as MAA or as microspheres, which once were labeled with ^{131}I and are now usually labeled with ^{99m}Tc, feathery particles (called *flocs*) of ferrous hydroxide labeled with ^{99m}Tc have also been used. This material forms a flocculated precipitate that incorporates ^{99m}Tc. The use of this material has been limited because of problems of adverse reactions. Patients sometimes flush when they are injected. The inorganic iron particles are more difficult for the body to remove than are the albumin particles. Of course, any particle of the correct size that can be labeled with radioactivity can be used for capillary blockade studies, but in the human body we are limited to materials that are nonantigenic and biodegradable. In animal research studies, other materials such as carbonized plastic microspheres or starch gel microspheres may be preferred because they are not readily metabolized and carried away from the point where they initially lodge. This gives the investigator greater flexibility in experimental design.

Most often the area being studied is the lung (Fig. 3-3), so the particles may be injected in the peripheral venous system, where the particles will be carried to the right heart and mixed well with the blood flowing into the lungs. The usual injection site is an arm vein. However, when the legs are suspected as the site of thrombosis, an isotope venogram is often done just prior to the lung scan. In these instances the tracer is injected into veins of the feet.

Lung scanning was first discovered when attempts to make colloidal particles of albumin failed. The investigators observed that when the colloidal particles aggregated, the radioactivity was localized in the lungs rather than the liver, as they had intended. They quickly realized that they had inadvertently discovered a way to visualize pulmonary perfusion and that the procedure would allow for the detection of perfusion defects caused by pulmonary embolism. Thus, ^{131}I **HSA** was macroaggregated and introduced as a radiopharmaceutical for lung scanning.

Both particle size and number are critical considerations in the preparation of lung-scanning agents. The particles must be large enough to be trapped quantitatively in the microcirculation; that is, all particles should be larger than the largest capillaries. They must be small enough so as not to be dangerous and not to be trapped too far upstream from the capillaries. Almost all particles greater than 15 μ are trapped in the lungs. Particles greater than 100
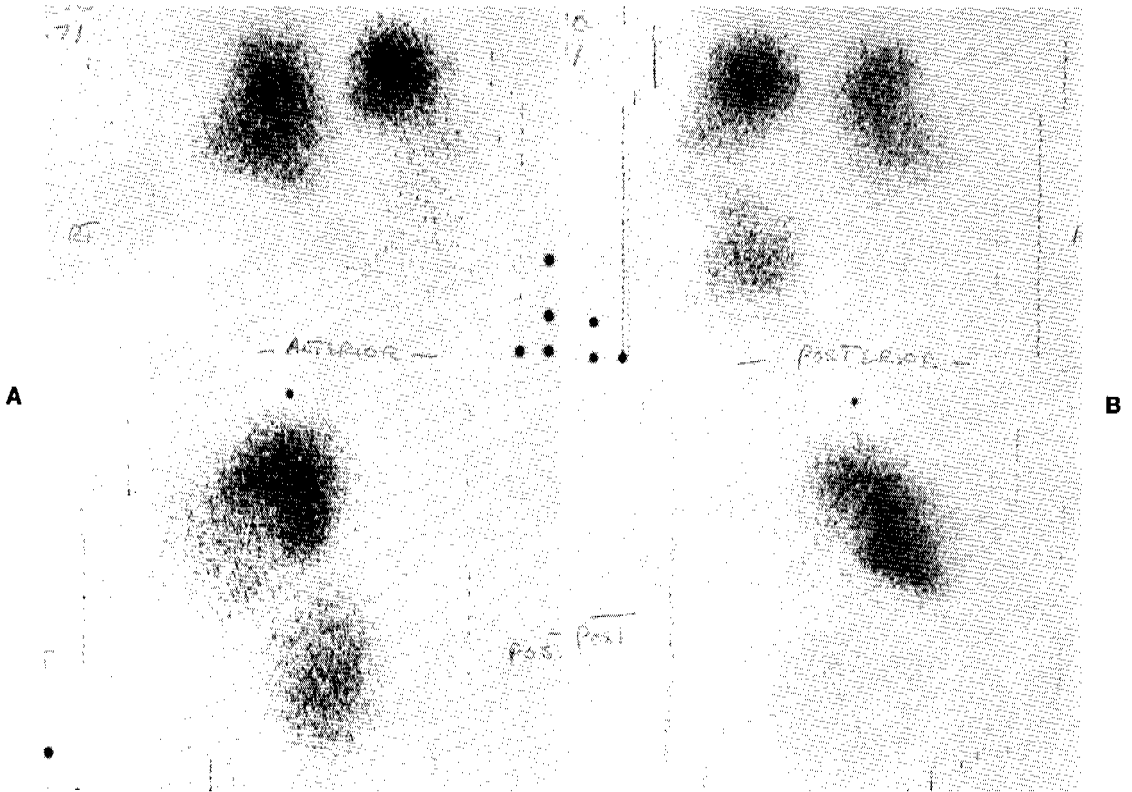
Fig. 3-3. Rectilinear scans of lungs after intravenous dose of ^{131}I macroaggregated albumin. Distribution of radioactivity within lungs is proportional to regional perfusion. Areas of decreased dot density on film correspond to regions of lung where perfusion is blocked by pulmonary emboli. **A,** Anterior and left lateral views. **B,** Posterior and right lateral views.

μ can cause vasoconstrictive responses on impaction in a small artery or arteriole. Thus, larger particles may alter perfusion patterns and in large numbers cause pulmonary hypertension. Ideally, particle sizes should all be greater than 15 μ with the mean size as near 15 as possible. Macroaggregated albumin with particles up to 90 μ is accepted for lung scanning. Albumin microspheres are available, with 35 μ the upper limit of particle size. Particle number is related to the number of particles per milligram. The number of particles is inversely proportional to the cube of the radius; that is, if the particle size is doubled, the number of particles per milligram decreases by a factor of eight. When too few particles are used, statistical parameters may lead to false positive results. When less than 4×10^4 particles are injected, a patchy scan may result from the expected

statistical variations in the distribution of the radioactivity. It is generally accepted that $1 - 1.5 \times 10^5$ is probably the best balance by having enough particles to also assure a true representative sampling of the distribution without excessively embolizing the pulmonary circulation.

Lung scanning is usually performed to aid in the diagnosis of pulmonary **emboli.** These mobilized blood clots **(thrombi)** very often originate in the veins of the legs or pelvis. They can block off perfusion to segments of the lungs and sometimes even block off a whole lung. The nonperfused areas show up on the scan as nonradioactive regions, while the rest of the lung tissue is radioactive. Of course, everything that causes a perfusion deficit causes a defect to be visualized on the lung scan. Other causes for perfusion deficits are pneumonia, fluid in

the pleural space, chronic obstructive lung disease, and acute asthma.

In addition to capillary blockade, radioactive particles are employed to view structures in other parts of the body, usually as an adjunct to a lung-scanning procedure. A lung-scanning dose may be injected in a leg or foot vein in order to see if there are areas in the leg where the particles appear to collect (Fig. 3-4). These may be areas that are partially closed off by thrombi or where fibrin is forming on the inner surface of a vein. Occasionally one sees such
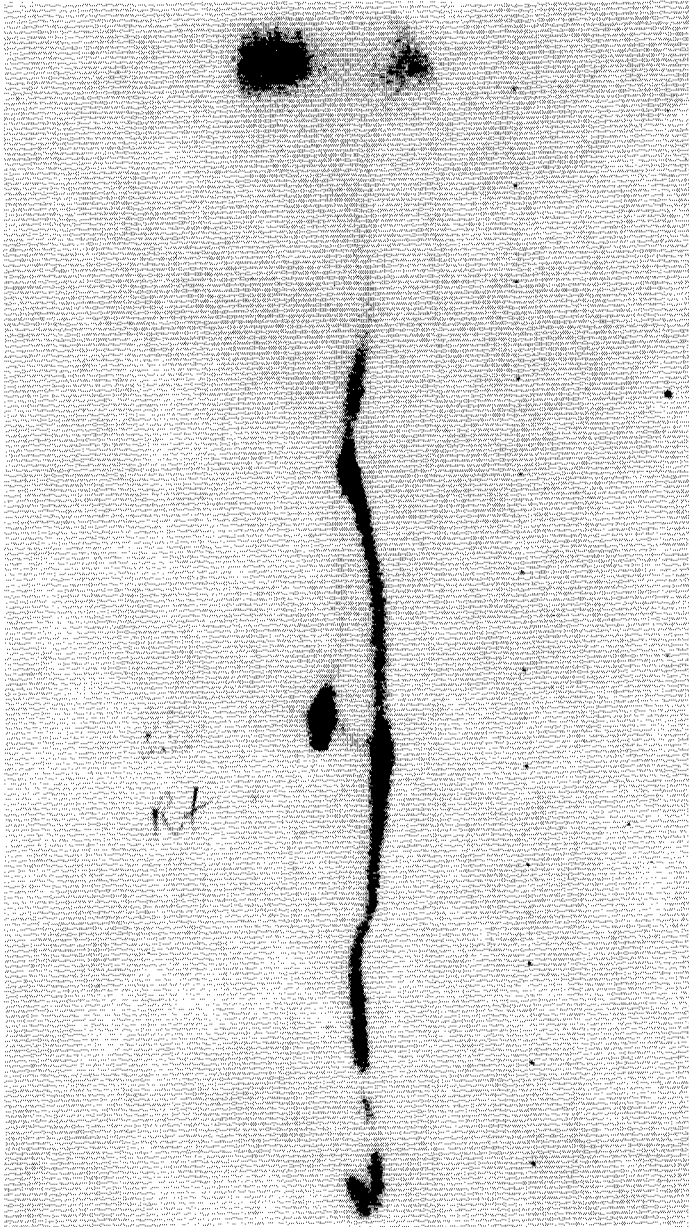
Fig. 3-4. Isotope venogram taken immediately after injection of ^{99m}Tc macroaggregated human *serum albumin* into vein in right foot. Movement of radioactivity up venous system and its appearance in lungs is seen in image.

an area of particle accumulation in the arm veins during a routine injection. These are frequently associated with indwelling venous catheters, which can cause irritation of the venous epithelium, followed by fibrin deposition and particle entrapment. The mechanism of accumulation is not capillary blockage; rather, it appears to be an adhesion of the particles to thrombogenic elements.

Particles may be injected to observe the flow of blood in the coronary arteries and used to help diagnose the areas that are not receiving blood at the time of injection. These areas may be **ischemic** or **infarcted.** The injections are usually carried out when a catheter is inserted into the coronary arteries for the purpose of obtaining a coronary arteriogram. Of course, the distribution seen may be a result of catheter placement or of the injection technique if either result in the particles not being well mixed with the blood prior to their reaching the capillaries. The arterial flow to the extremities or the head may also be studied by this same technique, that is, injecting radioactive particles through a catheter directly into an artery.

Rather than looking at specific areas for

Fig. 3-5. Rectilinear scan, posterior view, performed on young adult after intravenous administration of ^{99m}Tc HSA microspheres. Appearance of radioactive tracer in kidneys is due to right-to-left shunting of particles through heart so that some microspheres bypass pulmonary capillary bed. (From Deland, F. H., and Wagner, H. N.: Atlas of nuclear medicine, vol. 2, Lung and heart, Philadelphia, 1970, W. B. Saunders Co.)

pictorial information, one may use particle techniques to get quantitative information. The lung scan can be quantitated to give the percent of the total perfusion that occurs in a particular area. If the patient is shunting blood around the lungs into the arterial side of the circulation, either through an arterial venous anastomosis or via a hole in the septum of the heart, the material intended for the lungs will go elsewhere. Since the kidneys receive much of the cardiac output, they will be visualized in cases of significant right-to-left shunting. The amount of radioactivity not localized in the lungs can be counted and compared to the lungs in order to quantitate the amount of shunting (Fig. 3-5). This same idea can be used to quantitate nutritional and shunted blood flow to any region. The region of interest determines the point of injection.

Phagocytosis

When certain types of albumin macroaggregates are broken down by the cells in the lung, they become smaller than red blood cells and can fit through the smallest capillaries and thus escape back into the circulation. To the body they appear to be foreign material, much as pieces of red cells might after the red cell had died and begun to break up. These foreign particles are coated by a plasma protein called an *opsonin*. Opsonized particles are recognized by the *reticuloendothelial cells* (RE or Kupffer cells) and are engulfed. These RE cells are found primarily in liver, spleen, and bone marrow. They function by grabbing onto materials of size range of about 50 to 4,000 μ and ingesting or phagocytizing the foreign particles, thereby removing them from the circulation. If the cell can digest the material, as in the case of albumin, it will; if it cannot, it simply holds onto it. Although these phagocytic RE cells exist normally in the liver, spleen, and bone marrow, they may be present and active in other organs in certain abnormal conditions. RE function allows us to use radiolabeled particles as tracers to study phagocytosis and to localize and visualize the organs where phagocytosis is taking place.

The liver-scanning agent that is most commonly used today is ^{99m}Tc sulfur colloid, pre-

pared by heating thiosulfate in the presence of acid and pertechnetate. This forms a sulfur colloid of 300 to 1,500 μ that tends to increase in average particle size with time. Stannous reduction can also be used to repair a ^{99m}Tc colloid. In the past, ^{198}Au colloid and ^{131}I HSA colloid (microaggregated albumin) were used for scanning. Gold colloid is a rosy-red solution containing both radioactive and stable gold isotopes. The ^{131}I-microaggregated albumin has the conceptual advantage of being made from a human product and as such is biodegradable and nonantigenic, but it has the distinct disadvantage, along with ^{198}Au colloid, of conferring far too large a radiation dose compared to the number of usable counts for scanning. In addition to those already mentioned, indium phosphate or hydroxide can be formed in colloidal-sized particles. These particles can be labeled with ^{113m}In or ^{111}In. ^{99m}Tc-labeled phytate is a solution that when injected forms a colloid with the Ca^{+2} ion in the blood. The ^{99m}Tc colloid formed in the blood is then picked up in the RE cells.

Functioning liver, spleen, and bone marrow can be imaged minutes after the intravenous injection of radioactive colloid (Fig. 3-6). Once the material is sequestered, the physical location of the radioactivity usually remains constant. It has been suggested that the size of the injected particles determines to some extent which of the three organs will be the primary site of sequestration, with small particles going more to the bone marrow, medium-sized particles more to the liver, and larger particles more to the spleen. The differences in electrochemical properties of the different sizes may also account for differences in biodistribution. Experimental verification of this idea has not been presented.

The RE cells are evenly distributed in the liver and spleen, spatially associated with the other cells found in these organs. One can study morphology (size and shape) of the organs, evenness of the distribution of the material, and the apparent relative amounts accumulated in each of the primary organs of RE function. A poorly functioning cirrhotic liver may have an uneven distribution of radiocolloid uptake; in addition, the spleen will usually collect more
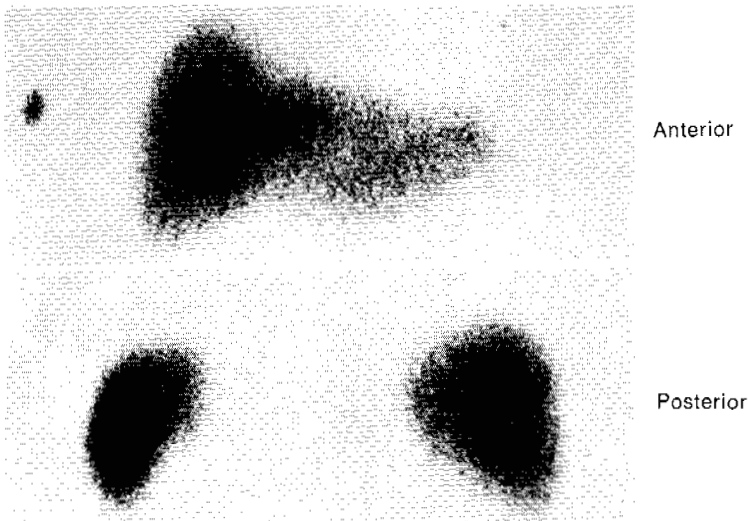
Fig. 3-6. Scintigram showing distribution of ⁹⁹ᵐTc sulfur colloid in liver and spleen. Upper image is anterior view; lower image is posterior view.

than its normal share of the dose, and the bone marrow will appear more prominently in the image than usual. This results from bone marrow expansion and its relatively increased avidity for the radioactive tracer, which in turn results in more radioactivity (counts) coming from the marrow as compared to the liver.

As an indicator of liver blood flow, with everything else remaining constant, one can study the rate of disappearance of colloid from the blood. Over 85% of the labeled colloid that is presented to a set of RE cells is trapped. This results in almost all the tracer being removed from the blood in its first pass through the liver. Thus, the rate of removal of the tracer from the blood is proportional to liver blood flow. The data from such a study are normally obtained from a probe aimed at the head. Rapid sequential counts are recorded and plotted on semilog paper. The longer time component is substracted from the shorter time component, and the initial disappearance constant is obtained (Fig. 2-8). This is the fraction extracted per minute. Patients with severely diseased livers have a slower blood clearance. To obtain baseline data, patients must fast and keep still before the examination.

One can also measure the RE system's capacity to phagocytize particles. To do this, the liver is challenged with larger and larger doses of nonradioactive colloid alternating with tracer amounts of the radiolabeled colloid. The rate of disappearance of each dose of tracer is measured. There are data to suggest that RE system capacity may be increased in bacteriologic infection and decreased in viral infection (Wagner and Iio).

Liver-spleen scanning doses of ⁹⁹ᵐTc sulfur colloid may be observed in static studies beginning 5 to 15 minutes after the injection. The biodistribution of the tracer may also be observed with serial Anger camera images. These dynamic studies are begun immediately after a bolus injection of the tracer. In this way one can use the inflow of ⁹⁹ᵐTc sulfur colloid to show the vascularization of the liver and spleen and then the deposition of the sulfur colloid to show the areas of RE cell function. Normally, the two functions ought to match; that is, the liver should be evenly vascularized and evenly populated with RE cells. If there is greater radioactivity in a particular location during the vascular phase of the study than during the static phase, a vascular lesion such as a tumor is indicated. Areas that have decreased activity on both studies may be cysts, abscesses, avascular tumors, or fatty infiltrates due to cirrhosis.
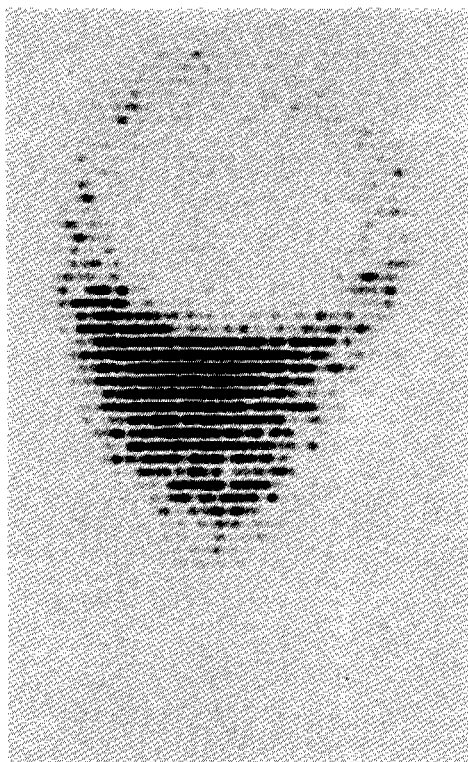
Fig. 3-7. Rectilinear scan of spleen after administration of ^{51}Cr-labeled heat-treated red blood cells. Large circular region of decreased dot density (*filling defect* in nuclear medicine jargon) seen in this left lateral view was caused by splenic cyst.

Cell sequestration

One of the functions of the spleen is to act as an inspection station and filter for red cells, that is, to remove (from the circulation) those cells which are no longer in prime condition. If a sample of the patient's red cells is labeled with a radioactive tracer and damaged slightly before reinjection into the patient, a splenic image can be obtained without interference from radioactivity in the liver. Usually a ^{99m}Tc sulfur colloid is also employed to obtain a liver-spleen image for comparison. The methods used for damaging the red cells must be mild, otherwise a liver image will also be obtained. One method is to damage ^{51}Cr-labeled red cells with heat: 50° C for an hour with gentle swirling. Another method is to treat the red cells with ^{197}Hg mercurihydroxypropane (MHP). Yet another method is to treat the cells with excess stannous

ion while labeling them with ^{99m}Tc. The most common instances for wanting to image the spleen without imaging the liver are (1) in cases where the left lobe of the liver cannot be well distinguished from the spleen and (2) in cases where the spleen has been removed, but where little accessory spleens, which could be hidden by the liver, are suspected. Fig. 3-7 shows an example of a spleen imaged in a patient with a cyst.

A diseased (hyperfunctioning) spleen may remove perfectly good red cells from circulation, causing anemia in the patient. The usual therapy is removal of the spleen, but the attending physicians like to be sure that they have identified the problem correctly. One method used in the diagnosis of this problem is a tracer study called *splenic sequestration*. Red cells are labeled without damage with ^{51}Cr and reinjected into the patient. At intervals for the next three weeks the radioactivity in the patient's spleen, liver, and precordium is reproducibly determined with a probe-type scintillation detector. Also, blood samples are taken. The radioactivity count ratios of the organs to the precordium or circulating blood pool are calculated to see whether the spleen-to-liver ratio rises beyond 2:1 (Fig. 3-8). The radioactivity per 1 cc of red cells in the blood samples is used to construct a graph of concentration of radioactivity in red cells versus time. This slope of the curve is increased when red cell survival is being shortened by hypersplenism. The disease is indicated by a shortened $T_{\frac{1}{2}}$, as shown in Fig. 3-9.

When a blood sample is withdrawn from a patient for labeling, the sample contains red cells of many different ages, some young, some old. Labeling of such a sample is called *random labeling*. If we wish to label red cells uniformly with respect to age, we must label them when they are created. To do this we give some radioactive precursor, which will be incorporated into all the cells as they are produced. One such material is iron. Radioiron produces cohort labeling, that is, labeling of cells all having the same age. Radioiron is not useful for splenic sequestration and red cell survival studies because the iron is recycled by the body and becomes reincorporated into further generations
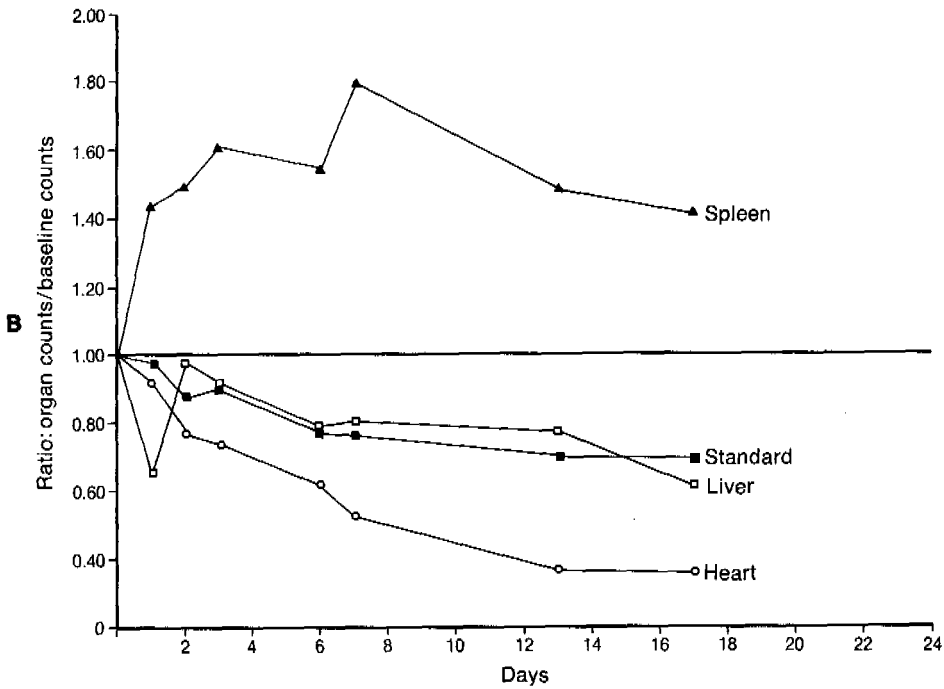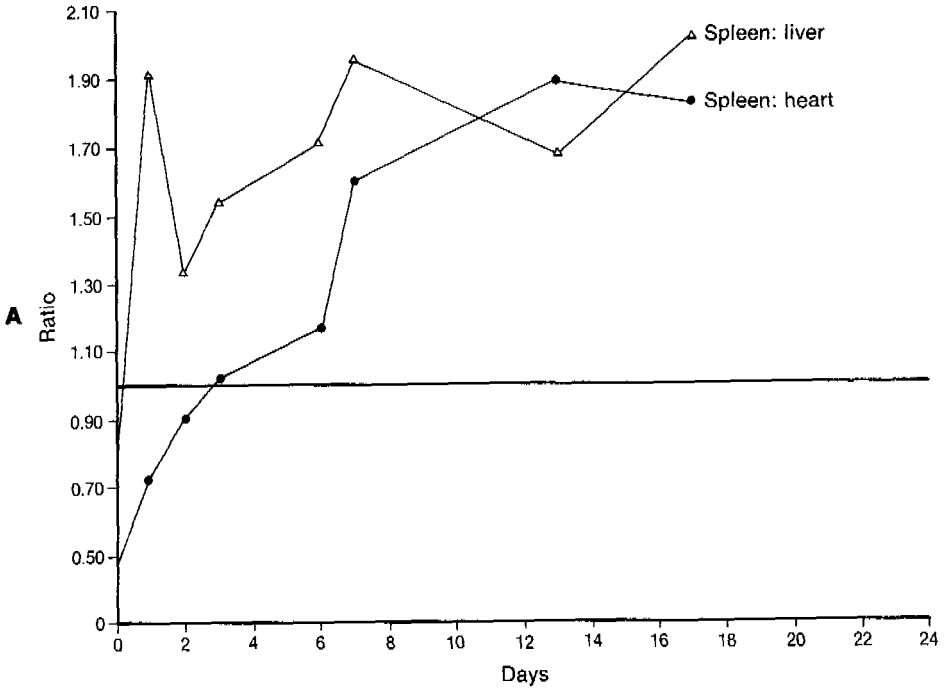
Fig. 3-8. Plot of radioactivity to determine relative uptake of tagged red blood cells in spleen compared to liver. **A,** Spleen-to-liver and spleen-to-heart ratios. **B,** Relative radioactivity in spleen, liver, and heart. These data were used to calculate ratios reported in upper figure.
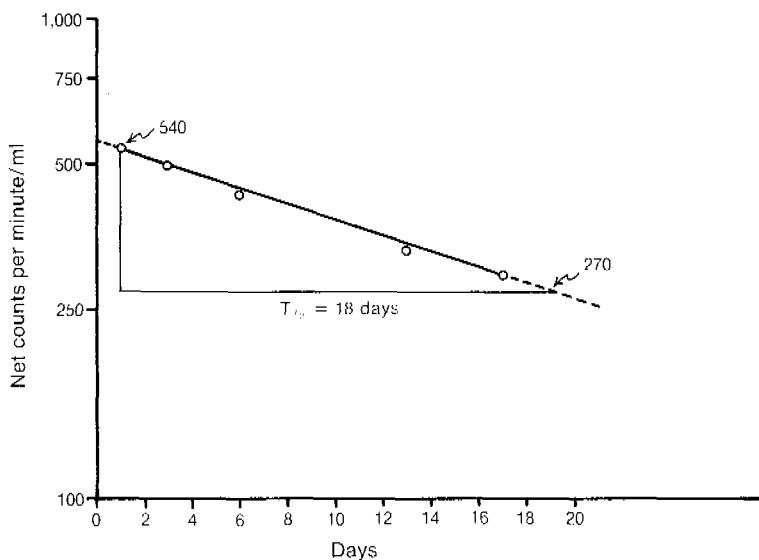
Fig. 3-9. Plot of radiochromium in RBCs measured for 2-week period. This gives $T_{1/2}$ and is used as indicator of red blood cell life.

of red cells. The normal half-life of a newly created set of red cells is 120 days, whereas the measured half-life of randomly labeled red cells is 27 to 35 days, depending on labeling techniques.

The spleen is also active in the screening and metabolism of other blood fractions, but less is known about the kinetics of their sequestration functions. White cells and platelets, appropriately labeled and altered, could probably serve as tracers for these splenic functions.

Active transport

Active transport involves labeling by the involvement of ordinary metabolic processes specific to individual organs. This mechanism can be used both to study function and to obtain images of specific organs. The example that comes to mind immediately is the use of radioactive iodine to study or treat the thyroid gland. Iodide introduced into the circulation, either from oral administration or by direct intravenous injection, is taken up by the thyroid and used to make thyroid hormones. The small amounts of the thyroid hormones are released into the circulation, where they serve as regulators of metabolic rates. Thus, radioactive iodine can be used as a tracer to follow the vari-

ous steps of thyroid hormone formation, storage, and use. Certain other negative ions can be used to study the first step of this process; the initial trapping of the iodine by the thyroid is mimicked by pertechnetate ion (Fig. 3-10). The same negative ions that concentrate in the thyroid are also concentrated by salivary glands and are excreted in saliva, as well as being concentrated by the gastric mucosa and excreted in the gastric juices. The scanning technique to locate Meckel's diverticulum is based on this mechanism of tracer localization.

The liver acts as a filter for removal of toxins from the body. If liver blood flow is unimpaired, the rate at which such materials are removed from the blood reflects liver function, in particular the activity of the polygonal cells of the liver. Lipophilic tracers, toxins, and certain dyes are cleared from the blood by the polygonal cells of the liver and secreted into the bile ducts that drain into the gallbladder. From time to time the bile is discharged into the small intestine. The gallbladder can be visualized when filled with a radiolabeled substance. The tracers are normally cleared from the gallbladder with a half-time of 7 to 8 minutes. The tracer appears in the duodenum within 20 minutes (Fig. 3-11). The most commonly used materials are ^{131}I rose bengal and [131]I
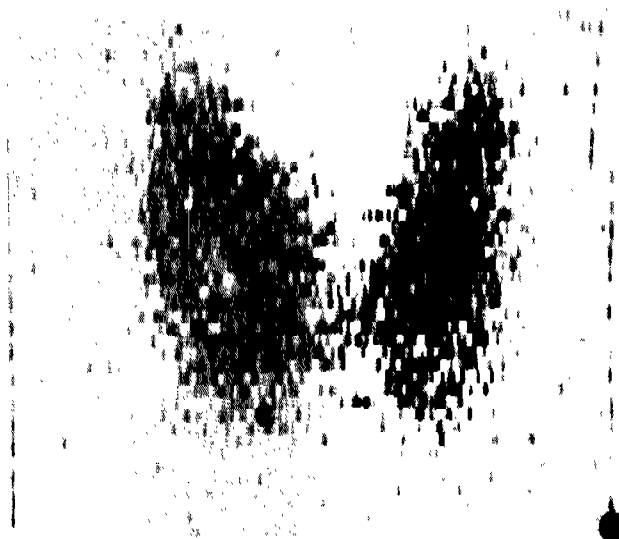
Fig. 3-10. Rectilinear image of thyroid made after administration of $^{99m}TcO_4^-$.
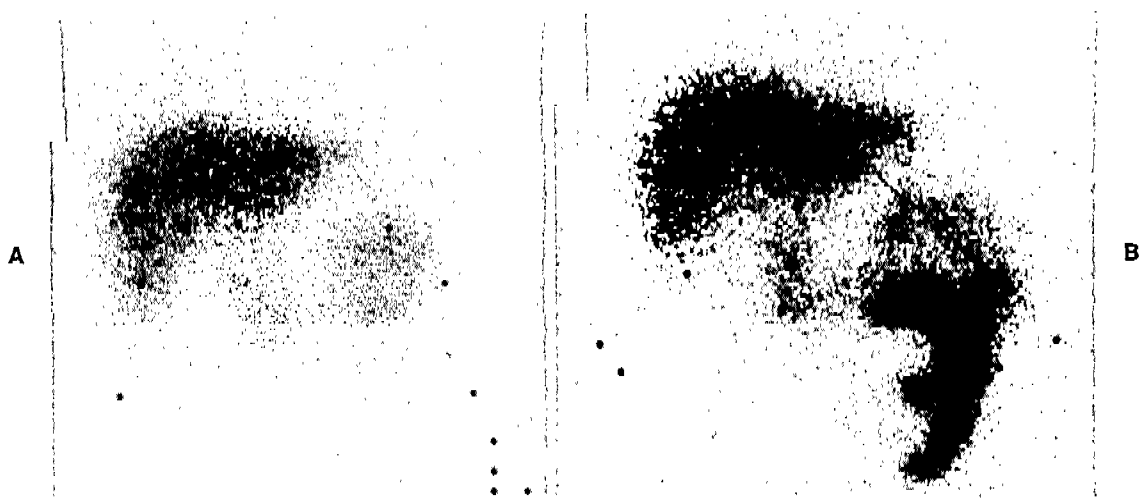
Fig. 3-11. A, Liver scan, anterior view, 1 hour after injection; radiopharmaceutical is ^{131}I rose bengal. **B,** Repeat image made 2½ hours after injection. Diagnosis: nonfilling gallbladder, patency of bile duct. (Gallbladder is not obvious on images; however, movement of tracer into gut is visualized.)

bromosulfophthalein (BSP), which are the same materials used in the dye clearance studies. Several ^{99m}Tc-labeled substances have been developed that are actively accumulated by the polygonal cells. These include dihydrothioctic acid, pyridoxylideneglutamate, *N*-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid, and kethoxal-bis (thiosemicarbazone); the structures of most of these compounds are shown in Fig. 3-12. When nonradioactive tracers are used, no pictorial information is obtained, and the measurements require collection of blood samples. The nuclear examination is done with sequential Anger camera images, either to study liver function or to assess the patency of the common bile duct.
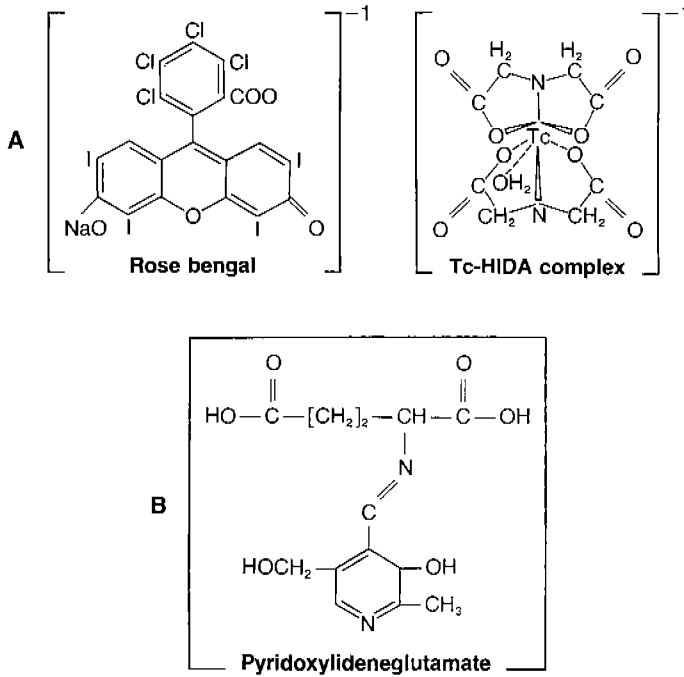
Fig. 3-12. A, Chemical structure of three tracers accumulated by polygonal cells and excreted into bile. Rose bengal is labeled with ^{123}I or ^{131}I. HIDA is labeled with ^{99m}Tc. **B,** Pyridoxylideneglutamate is labeled with ^{99m}Tc; however, only structure of unlabeled complex is shown here.

As a filtering organ, the kidney has no peer. Its mechanisms for filtering the blood, saving the desirable materials, and concentrating the undesirable materials and sending them out are very complex. Some of its filtering is accomplished by active transport. This mechanism is required for selective removal of materials from the liquid presented and their subsequent excretion into the urine. The renal tubules are able to sort the materials in the glomerular filtrate into those to be reabsorbed into the blood and those to be excreted into the urine. Materials such as ^{123}I orthoiodohippurate (Fig. 3-13) are actively secreted by the renal tubules and passively, but only partially, reabsorbed into the blood. Technetium can be complexed to substances such as gluconic or glucoheptonic acid (Fig. 3-14) to produce a tracer suitable for study of the kidneys.

Active transport mechanisms have not been useful in pancreatic studies. The pancreas has only been imaged so far by presenting it with materials that it can use in the synthesis of digestive enzymes, such as ^{75}Se selenomethionine and various amino acids labeled with
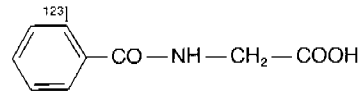
Fig. 3-13. Chemical structure of ^{123}I orthoiodohippuric acid.
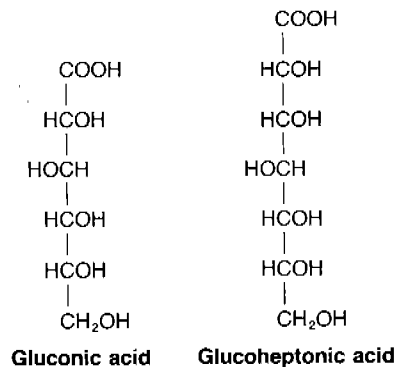
Fig. 3-14
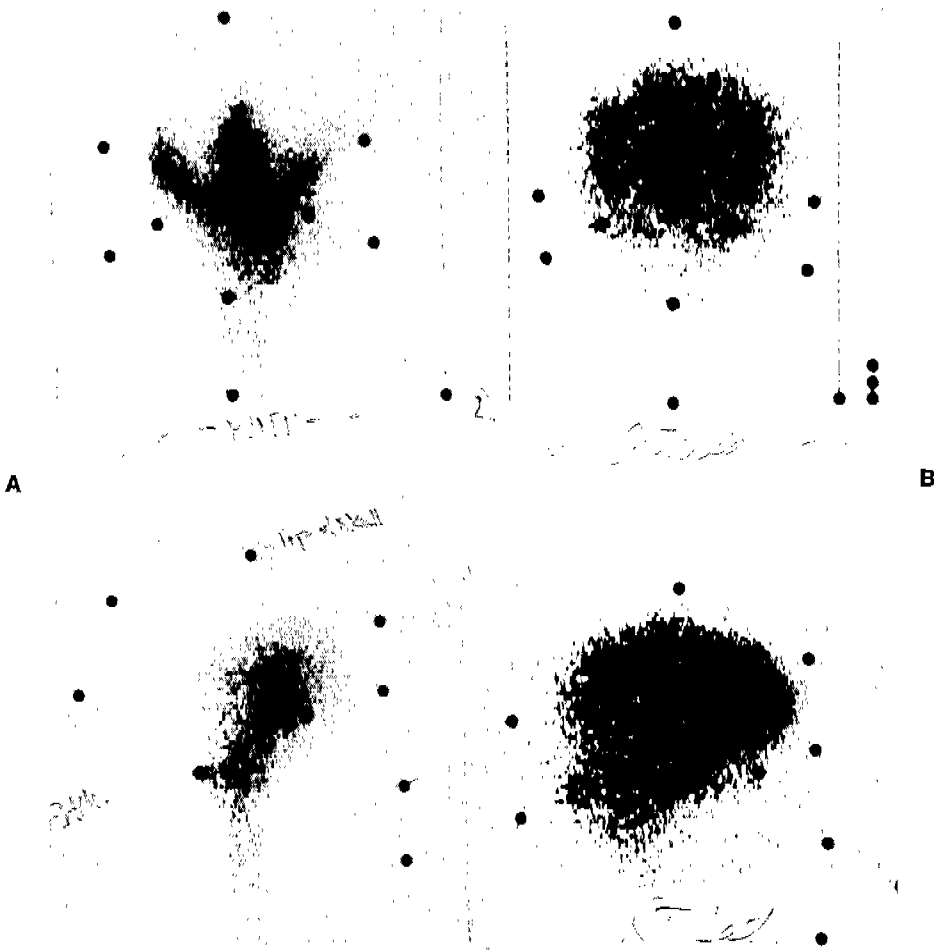
Fig. 3-15. A, Cisternogram images made 3 hours after injection of ^{111}In DTPA into spinal fluid. Upper images are anterior view; lower right image is lateral view. **B,** Same views made at 24 hours. Diagnosis: normal.

either ^{13}N or ^{11}C (positron emitters). The isotopes are concentrated because they are rapidly converted from a diffusible substance into large nondiffusible proteins, that is, the pancreas presents to the tracer a downhill concentration gradient.

In summary, using tracer principles, we can study the active transport functions of a number of vital organs. Our techniques permit both organ imaging and quantitative assessment of relative regional function.

Compartmental localization

The body contains several well-defined compartments, such as the blood circulatory system, the cerebrospinal fluid (CSF) space, the

airways of the lungs, the gastrointestinal (GI) tract, and the renal outflow system. It is readily possible to introduce a radioactive tracer into these systems that under ordinary circumstances will not diffuse out or be removed by active transport. With such a tracer we can study the boundaries and parameters of the system. The blood can be studied as to the amount of each of its constituents. These are the volume studies such as determination of plasma volume and red cell mass. It can be studied for its dynamics, either on a first-pass basis as the material is on its way to another location or on a continuing basis as one studies the parameters and images of blood flow in the heart using ^{99m}Tc-labeled red cells or

albumin. The CSF space has been examined using materials similar to its fluid, such as ^{131}I-albumin solution or materials that should follow its fluid, such as ^{111}In DTPA (Fig. 3-15). If there are leaks in the membranes, they will be seen by the visualization of the tracer outside the boundaries of the normal fluid space. For example, ^{51}Cr-labeled red cells can be perceived when they are leaking into the GI tract, or CSF can be detected when it is leaking out of the CSF space into the nasopharynx. Narrowings and blocks to normal flow within a compartment can also be visualized.

The timing of material movement through the GI tract may be determined. Gastric tracer studies employ insoluble ^{99m}Tc or ^{113m}In tracer and use Anger-camera imaging or serial scintillation probe measurements to localize the stomach and determine gastric reflux or gastric emptying rates. Any one of a number of agents may be used to study reflux of urinary bladder contents up the ureters to the kidneys.

Compartmental analysis is useful in considering the distribution of any tracer within the body. The kinetic equations derived from analysis of the various compartments of distribution and the possible pathways between the compartments can be diagnostically useful. Compartment analysis is a way of evaluating kidney function. A ferrokinetic study is a way of evaluating the hemopoetic function.

Simple or exchange diffusion

This section discusses all the remaining kinds of localization that are accomplished by passive mechanisms, in which the amount of material getting into a particular location is not governed by an any more exciting principle than that it happened to get into the spot in some concentration and did not get out. A real-world example of this might be a bolus of muddy water going down the Mississippi River. As it flows down the river, some of it gets into the swift water, gets ahead of the center, and is washed out quickly. However, some of it gets caught in meandering eddies off to one side and continues to circle lazily there after the main part of the muddy water has passed by. The mainstream is clear again, whereas the eddies are still muddy. This phenomenon has sometimes been referred to as the swamp effect and is often used to get differential tracer concentrations that permit imaging of structures and lesions within normal brain tissues.

^{99m}Tc pertechnetate and other materials such as ^{99m}Tc DTPA, ^{131}I albumin, and ^{197}Hg chlormerodrin are used for brain scanning because all permit visualization of brain lesions by the swamp effect. The eddy is created by defects in the blood-brain barrier that allow the scanning agent to diffuse into the lesion. The tracer does not readily diffuse back and so is left behind as the agent is cleared from the blood (Fig. 3-16).

Diffusion is probably the first step leading to localization of bone-imaging agents. The tracers diffuse from the blood into the extracellular fluids (ECF), including the fluids that bathe the surfaces of the bone mineral. Once a tracer like ^{99m}Tc pyrophosphate is exposed to the bone mineral, it is rapidly fixed to the solid phase of the bone crystal surfaces. This rapid fixation acts to keep the ECF concentration low, thereby maintaining a concentration gradient favorable for the continued movement of the tracer from the circulation to the ECF.

Thallium ions are concentrated in the myocardium by a combination of mechanisms, including exchange diffusion. Tl^{+1}, like K^+, is actively pumped into muscle cells by an ATPase-driven pump. Once intracellular, the Tl^{+1} is diluted in the relatively high intracellular concentration of K^+ ions. Thus, the efflux of ions during muscular contractions will be predominately K^+. In essence, it takes the Tl^{+1} longer to find a way out of the cells than it took to find a way in because of the difference in intracellular and intercellular concentrations of K^+ (Fig. 3-17).

Missing mechanisms

The preceding mechanisms provide a useful framework to try to conceptualize the mechanisms of action of the various agents used in nuclear medicine. They may be useful to us in our attempts to find new agents as well as to help us explain the pathophysiology observed with our tracer studies.

It should be obvious by now that most of the studies of nuclear medicine have not fit exactly
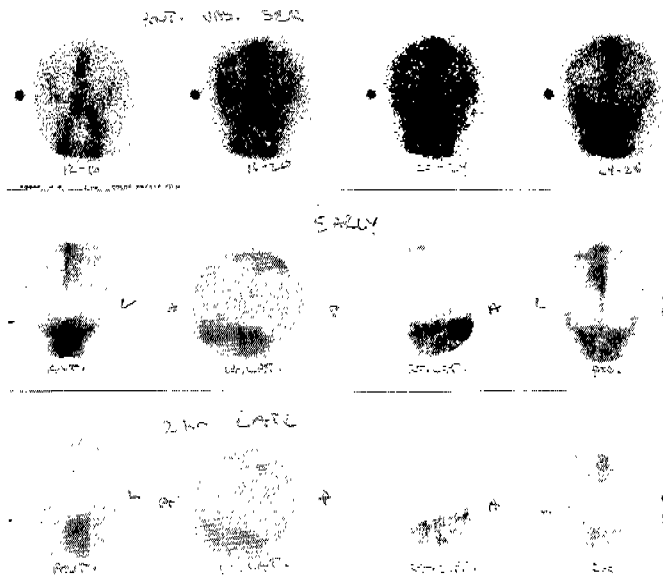
Fig. 3-16. Series of brain scintigrams. Upper row of images shows flow of tracer into head. Middle row shows early views; lower row shows delayed views taken 2 hours after injection. Diagnosis: glioblastoma multiforme.

60° LAO
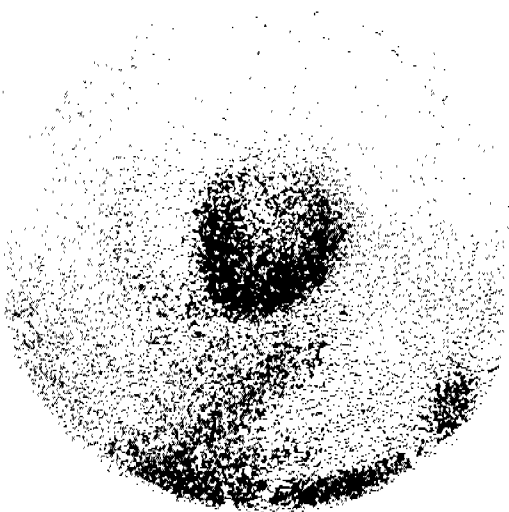
Fig. 3-17. Scintigram of normal myocardium. Radiopharmaceutical used was [201]TlCl. (Courtesy Presbyterian Hospital, Albuquerque, N.M.)
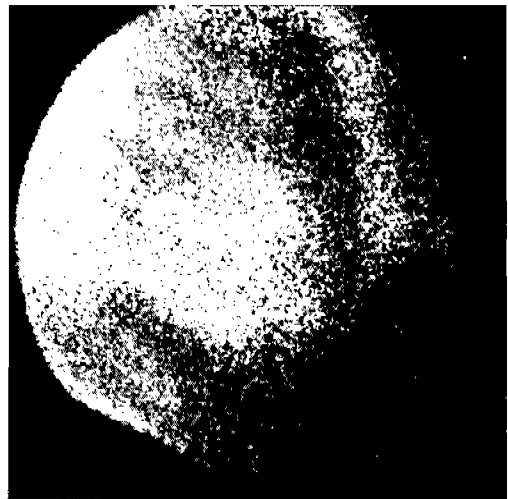
Fig. 3-18. Scintigram of infarcted myocardium. Radiopharmaceutical used was ^{99m}Tc pyrophosphate, which also localizes in bone; thus ribs are also visualized. (Courtesy Presbyterian Hospital, Albuquerque, N.M.)
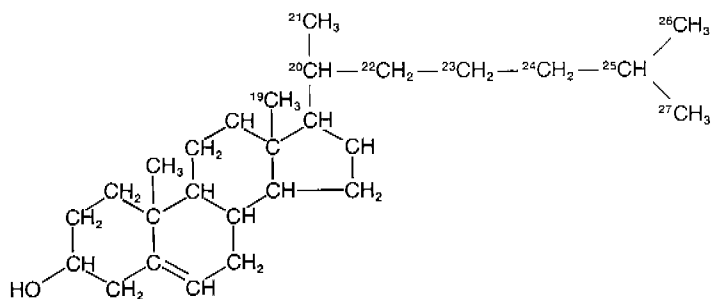
Cholesterol

Fig. 3-19. Chemical structure of cholesterol and two radioactive analogs of cholesterol that can be used to image adrenal glands.
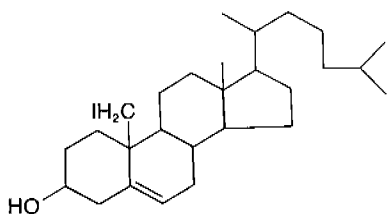
Iodocholesterol
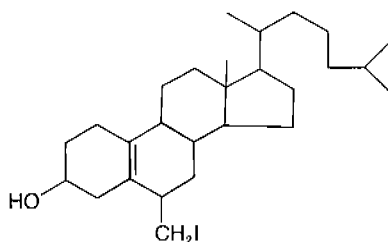
Iodomethylnorcholesterol

into one of the previous six categories. The human body's response to tracer substances is a great deal too complicated to be described by six mechanisms. The action of the kidneys, for example, is far too complicated to be adequately treated with these simplistic mechanisms. Often there is evidence to suggest both active and passive phases in the localization of a particular material. This complexity will appear to grow as nuclear medicine grows and more facts are discovered about the systems we are evaluating (Figs. 3-18 and 3-19).

Blood flow and tracer localization

The uptake or clearance of a tracer from its site of localization is highly dependent on blood
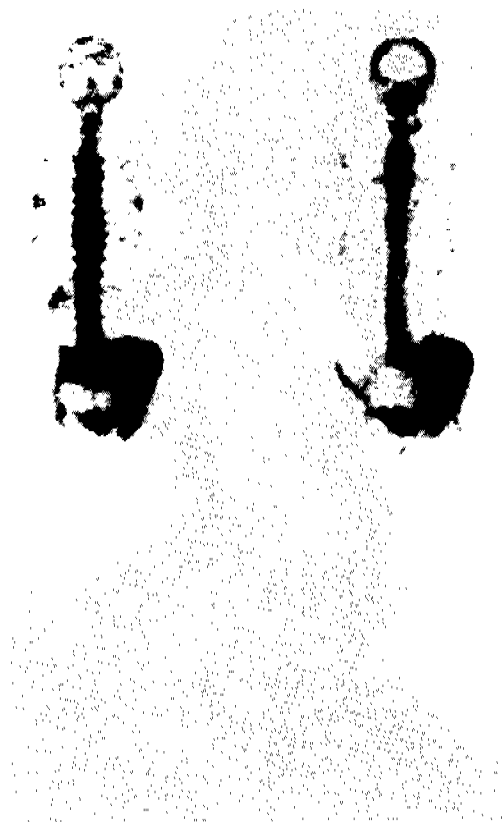
Fig. 3-20. Bone scan showing abnormal distribution of ^{99m}Tc methylene diphosphonate because of Paget's disease of bone in left ilium and pubic bones. Scan was performed on Cleon imager 7½ hours after injection.

supply to the region. The total amount of tracer deposited at any site depends on (1) the concentration of tracer in the blood perfusing the site, (2) the blood flow to the site, and (3) the efficiency of the localization mechanism at the site. The relationship between these factors is given in the following equation:

$$\text{Instantaneous uptake} = ecF$$

where e = extraction efficiency
     c = concentration in blood in μCi/ml
     F = blood flow in ml/min

With most of the currently used tracers, extraction efficiencies in the regions of interest approach unity. If a colloidal particle gets into the liner, it will most likely be engulfed by an RE cell; if an iodine ion gets into the thyroid gland, it will most likely be trapped; if a molecule of DTPA gets into a kidney, it will most likely be filtered. Thus, the uptake of a tracer in the target organ is usually limited primarily by blood flow and by the amount of the tracer in the blood perfusing the target organ. Bone uptake of ^{99m}Tc phosphate–type complexes illustrates this phenomenon. Diffusion of these tracers from blood into ECF and movement from ECF to the bone mineral are relatively fast so that regional bone blood flow becomes the primary determinant of tracer localization. We see a high uptake of these tracers in joints of growing children because blood flow to the zone of growth is high. Metastatic lesions are also characterized by increased blood flow. The associated acceleration of bone mineral turnover may indeed result in increased extraction efficiencies, but extraction efficiency is already high. By referring to the preceding equation, we can appreciate that an increase in extraction efficiency from 70% to 90% will have less influence on tracer uptake than will a doubling of blood flow. The point of this discussion is that blood flow must not be neglected in any analysis of a tracer's biodistribution (Fig. 3-20).

Suggested readings

Rhodes, B. A., and Bolles, T. F.: Albumin microspheres; current methods of preparation and use. In Subramanian, G., Rhodes, B. A., Cooper, J. F., and Sodd, V. J., editors: Radiopharmaceuticals, New York, 1965, Society of Nuclear Medicine, Inc.

Saba, T. M.: Physiology and physiopathology of the reticuloendothelial system, Arch. Intern. Med. **126:**1031-1050, 1970.

Wagner, H. N., Jr.: The search for nuclear magic bullets. In Subramanian, G., Rhodes, B. A., Cooper, J. F., and Sodd, V. J., editors: Radiopharmaceuticals, New York, 1975, Society of Nuclear Medicine, Inc.

Wagner, H. N., Jr., and Rhodes, B. A.: Radiopharmaceuticals. In Wagner, H. N., Jr., editor: Principles of nuclear medicine, Philadelphia, 1968, W. B. Saunders Co.

Design criteria

Design criteria for radiopharmaceuticals are discussed in order that one may see how currently used radiopharmaceuticals meet these criteria and how new radiopharmaccuticals might be designed to better meet these criteria. One essential principle central to the whole field of diagnostic medicine is that each examination should be performed in the safest and most effective way. Each topic in this discussion addresses a facet of the problem of matching the design of radioactive tracers to meet the demands of diagnostic medicine.

Physical characteristics

The physical characteristics of the nuclide should be within certain limiting criteria to be considered for inclusion among the ranks of nuclides used in nuclear medicine. In order to keep the radiation exposure to a minimum, the properties of half-life and radiation should be used to advantage (Fig. 4-1). The optimum physical half-life is 0.693 times the time at which the study is performed. If the measurement is made 100 minutes after tracer administration, the ideal isotope for the study would have a half-life of 69.3 minutes. This criterion maximizes the counts collected for use relative to those which are wasted in radiation dose to the patient both before and after the examination is carried out. It should be obvious as well that the shelf-life of the material is determined by its physical half-life, so nuclides with ultra-short half-lives cannot be held for future use. Thus, these tracers must be formulated and transported to the point of administration before they are spent by radioactive decay. For example, measurements 2 weeks after tracer administration cannot be obtained using nuclides with a 1-hour half-life. Likewise, examinations an hour after tracer administration should not be performed using a nuclide with a 2-week half-life.

The energy of the nuclide should be suitable for the detection device being employed (Fig. 4-2). If the Anger camera is used, the optimum energy is about 150 kev for maximum absorption by and maximum generation of light photons within the crystal. Energies from 80 to 400 kev are possible, but spatial resolution is lost on the low end, and sensitivity is lost at the high end of this energy range. Furthermore, the higher the gamma-photon energy, the heavier the collimators that must be used. If the rectilinear scanner is used, its thicker crystals permit the use of higher energies because thick crystals have relatively higher photoelectric absorption efficiencies; thus, energies from 100 to 500 kev are acceptable, including positron-emitting nuclides with a gamma photon at 511 kev. If a well-counting device is used for sample counting, lower gamma-ray energies are permitted because the photons do not have to escape the body in order to be counted. Gamma rays of higher energies are also possible; thus, energies from 25 to 550 kev are efficiently detected in a well counter. With these detectors, even gamma-ray emitters with photon energies up to 1.5 mev are acceptable, although the detection efficiency falls off appreciably at these higher energies. Fig. 4-3 shows detection efficiency for different-sized crystals as a function of gamma-ray energy. For probe detection, as used in thyroid or spleen counting, the energy must be sufficient to allow most of the gamma rays to reach the detector; thus, the acceptable range is 80 to 550 kev. It is important to point out here that even in an organ as close to the surface as the thyroid, it is not possible to accu-
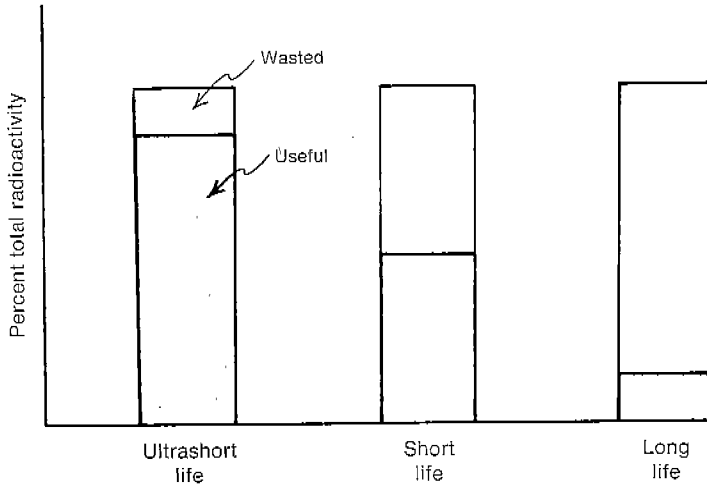
Fig. 4-1. Half-life of radionuclide is one determinant of radiation exposure. With ultrashort-lived isotopes, high portion of decay occurs during observation period to give high proportion of useful radiations. With long-lived isotopes, radioactive decay continues long after observation period to give high proportion of wasted radiations.
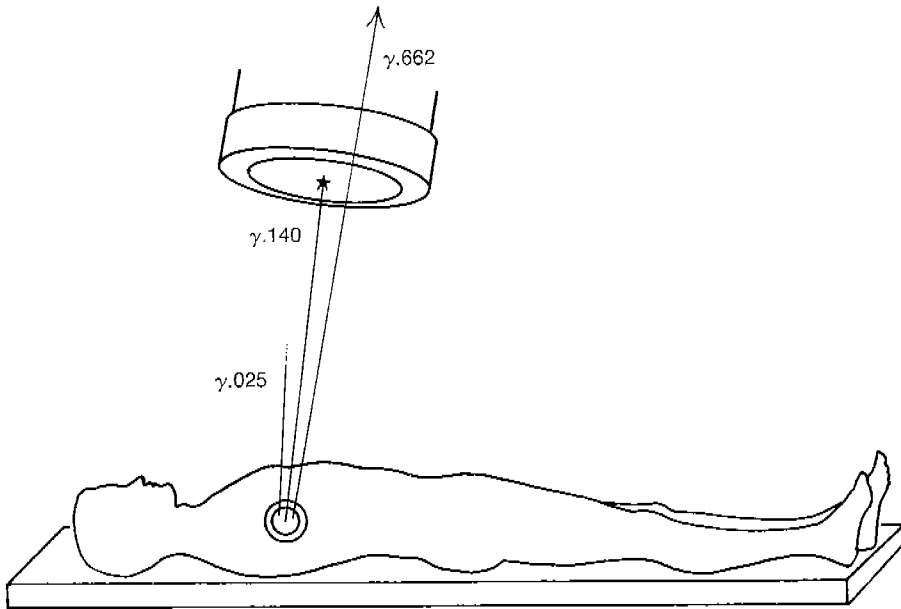
Fig. 4-2. When gamma-ray energy is low, as in case of radionuclides like [125]I (0.025 kev), high fraction of gamma rays are attenuated before they reach crystal. When gamma-ray energy is high, as in case of radionuclides like [137]Cs (0.662 kev), high fraction of gamma rays pass through detector and are therefore undetected. When gamma-ray energy is intermediate, as in case of radionuclides like [99m]Tc (0.140 kev), probability of detection is maximized.
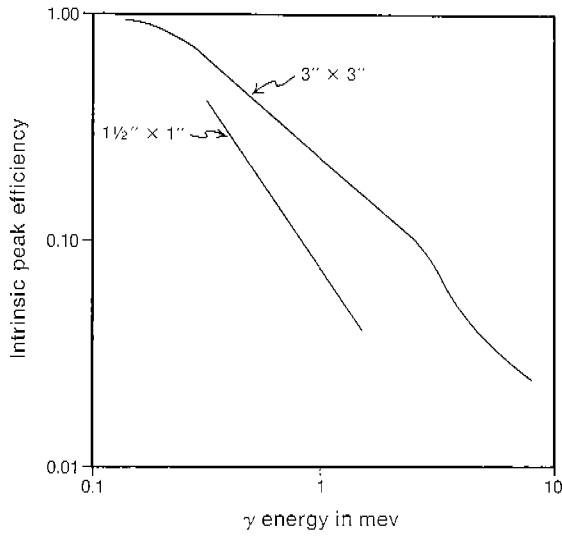
Fig. 4-3. Relationship between gamma-ray detection using NaI(Tl) crystal detectors and gamma-ray energy.
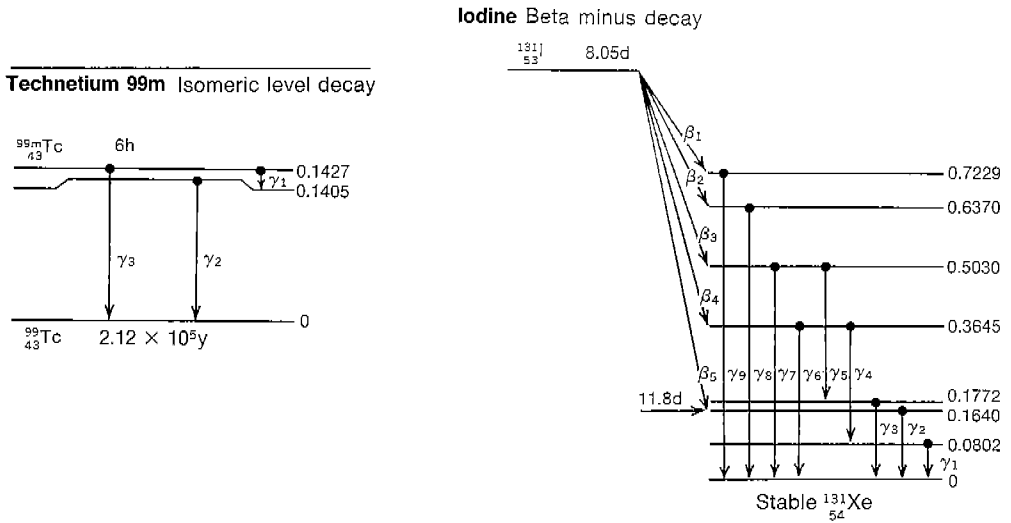
Fig. 4-4. Decay schemes for two nuclides commonly used in nuclear medicine. ^{99m}Tc has physical characteristics that are much closer to ideal than does ^{131}I. Use of ^{131}I is decreasing, whereas that of ^{99m}Tc is increasing.

rately measure uptake of the radioactivity when using a low-energy nuclide like ^{125}I without accounting for the depth of the thyroid in the neck. The overlying tissues will attenuate many of the photons emanating from the gland.

Ideally, the principal photon, with an energy in the optimum range, should be the only emission from the decaying nucleus. There should be no gamma radiation that is not in the energy peak which is being detected, and there should be no alpha or beta radiation at all. It is also preferred that there is no internal conversion path-

Camera type	Principally useful isotopes														
Anger	Cr 51 27.8d	Co 57 271d	Ga 67 78.2h	Br 77 56h	Kr 81 13s	Tc 99m 6.007h	In 111 2.82d	In 113m 1.66h	I 123 13.1h	Xe 127 36.41d	I 131 8.065d	Xe 133 5.27d	Yb 169 31d	Hg 197 64.1h	Pb 203 52h
Positron	C 11 20.4m	N 13 9.99m	O 15 122s	F 18 109.8m	Ga 68 68.3m	Rb 81 32m|4.7h									

Fig. 4-5. Listing of some of more commonly used gamma-emitting and positron-emitting radionuclides.
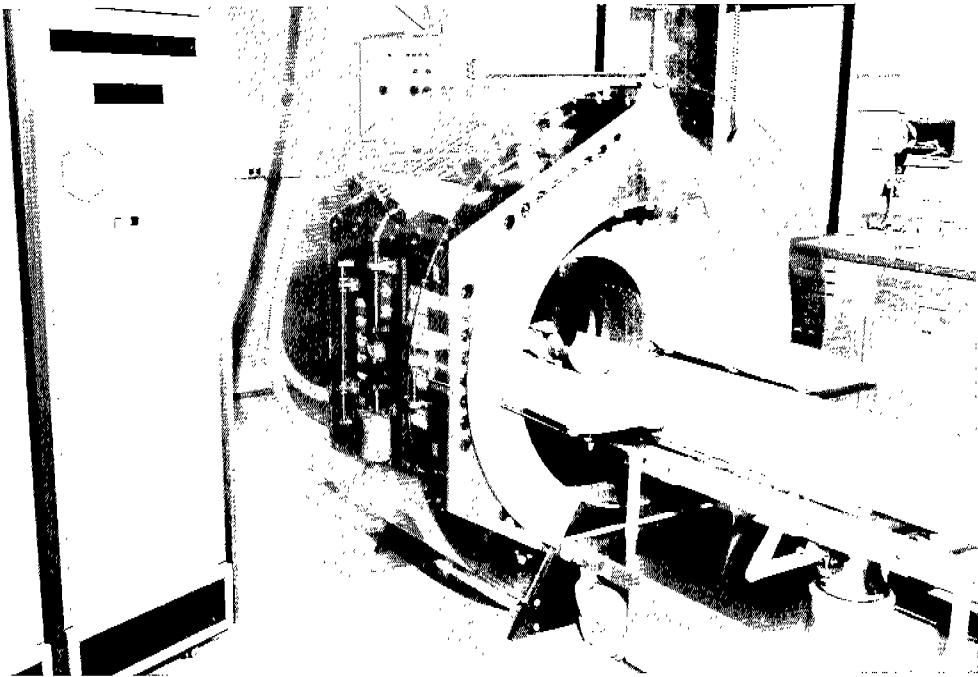
Fig. 4-6. PETT IV Scanner at Washington University Medical School. (PETT is short for positron-emission transaxial tomograph.) (Courtesy Washington University School of Medicine, St. Louis, Mo.)

way competing with the gamma emission. The decay products themselves should not have undesirable radiation or localization. These are very difficult criteria for the nuclides to be stacked up against. Isomeric transition and electron capture are the two optimal decay pathways. Actually, ^{99m}Tc ($T_{\frac{1}{2}}$ = 6 hours, 140 kev) is nearly ideal for examinations that take a day or less to perform. It is less than perfect when compared to some of the criteria later in the chapter. There are few suitable nuclides for examinations requiring more time to complete. A

perusal of the list of the nuclides in use unearths many whose characteristics are far from optimum, such as ^{131}I and [51]Cr. [131]I has an 8-day half-life, many beta rays, and nonuseful gamma rays; ^{51}Cr has a 27.8-day half-life (acceptable for 3-week studies but not really for 1-week studies) with only 8% of the energy per decay occurring in the 324 kev gamma energy peak, which is the one that is counted. Fig. 4-4 compares the decay scheme of ^{99m}Tc to [131]I.

It goes almost without saying that it would be ideal for the material to be inexpensive, easily produced in quantity, of high purity on production, and readily available to all nuclear medicine laboratories.

The list of usable nuclides will be expanded somewhat when positron detection devices come into common use (Fig. 4-5). Their installation in a clinic would encourage the use of positron emitters for all examinations. This is less confining than you might imagine because there are many positron emitters. Their half-lives vary, but their energies are the same: 511 kev. An **accelerator** close by for the production of the short-lived materials and a synthetic facility between the accelerator and the clinic become necessities for the production of the needed chemical species and for the formulation of the radiopharmaceutical. Fig. 4-6 shows a positron-emission transaxial tomograph, which is used for imaging studies employing positron emitters.

Chemical and biologic characteristics

To continue the list of required properties, we proceed to examine some that perhaps reflect less the characteristics of the instrument and more the safety of the patient and the con-
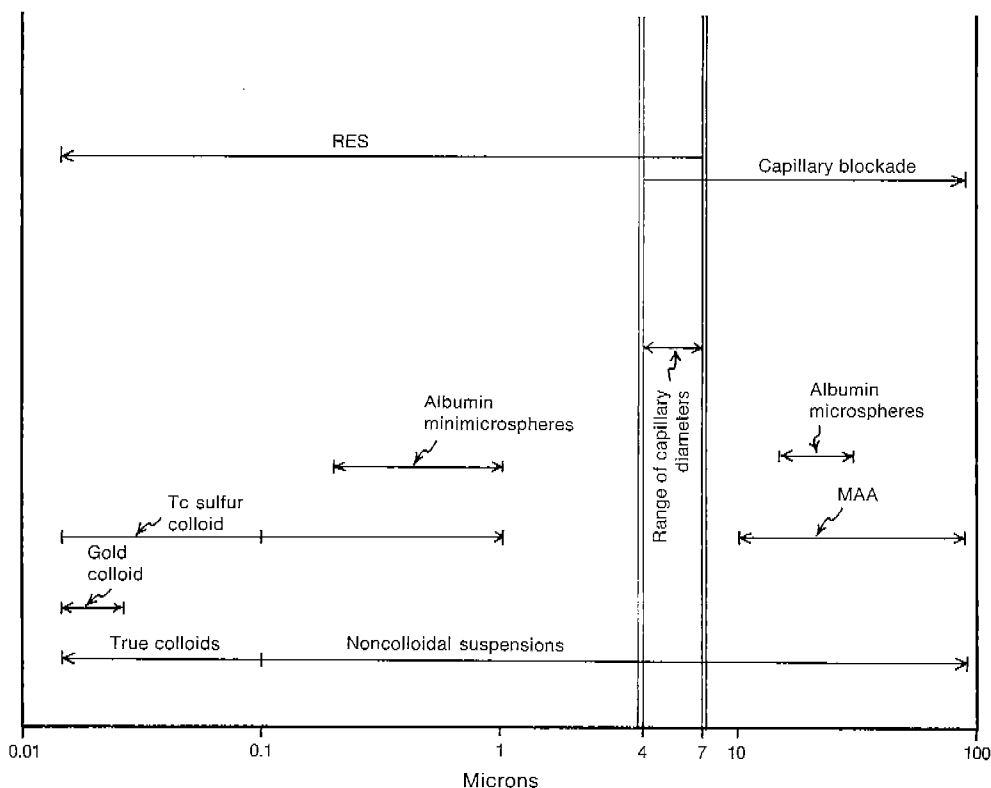
Fig. 4-7. Particles are removed from bloodstream primarily by RES or by capillary blockade. This drawing allows reader to compare size ranges for different particulate radiopharmaceuticals to size of capillary and to colloids.

venience of the radiopharmacist. In order to formulate patient doses in small injectable volumes and to obtain high count rates, it should be possible to achieve high specific activities, that is, a large amount of radioactivity per gram of material. This we should be able to accomplish without the addition of a nonradioactive **carrier** and without the presence of undesirable radionuclides.

The dosage form of the tracer must match the performance criteria dictated by the intended use of the tracer. The physical characteristics of the radiopharmaceutical, such as particulate size and charge, solubility in water and fat, molecular weight, and affinity for blood elements, all have to be carefully considered during its design. For example, if the study requires a particulate radioactive species, as in the case of RE studies, the radionuclide of choice must be changed from a **solute** to a solid, and the solid phase stabilized as a **colloid** suspension.

Colloidal particles are of a size that normally does not settle out of solution (Fig. 4-7). In more concentrated solutions they can be observed indirectly using the Tyndall effect; that is, the particles cannot be seen directly, but their light-scattering effect is visible. Fortunately, a colloidal suspension of almost any nuclide can be prepared. Unfortunately, most colloidal suspensions change appreciably with aging. As you know from the previous discussion on mechanisms of localization (Chapter 3), particulate matter is concentrated, depending on size, in either the lungs or the liver and spleen. Because of aging effects on particle size distribution, a colloidal suspension might be satisfactory for RE studies at 9 A.M., but when injected at noon it could exhibit an obvious uptake in the lungs. This happens when the natural tendency for particles to grow larger with time is not adequately checked by the use of colloid stabilizers. Stabilizers, like serum albumin or gelatin, coat the particles with a charged protein monolayer and thereby inhibit contact interactions between the particles. This inhibits particle growth.

Colloids can be precipitated by changing the
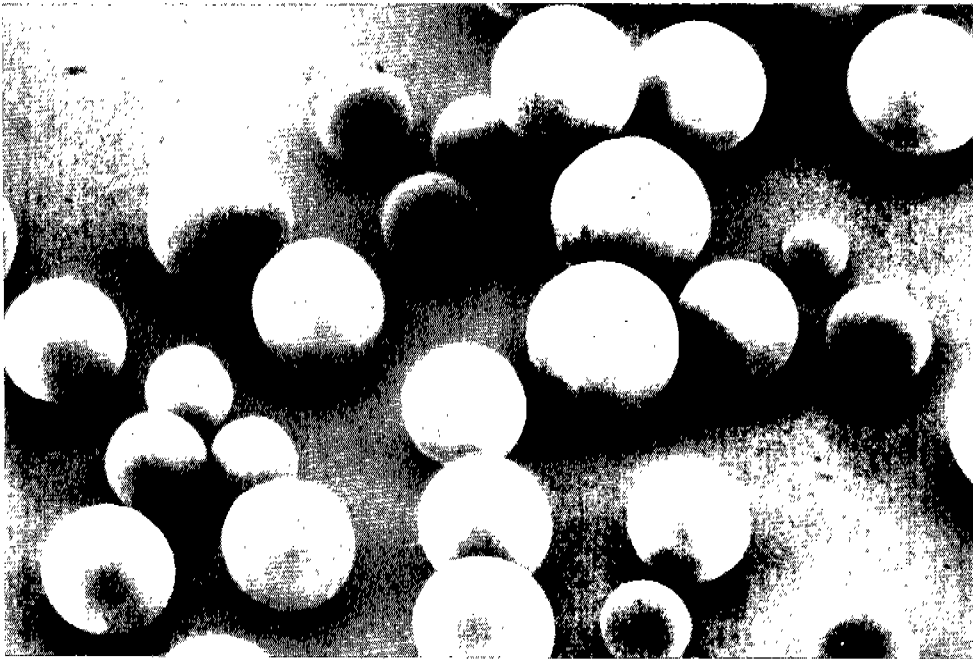
Fig. 4-8. Scanning electron micrograph of human serum albumin microspheres. ($\times 1,000$.)

electrochemical conditions of the solution. Just as a colloidal form of any nuclide can be prepared to create a tracer for RE studies, a precipitate of any colloid can be prepared to create a tracer for capillary blockade studies. The requirements for nonantigenicity and biodegradability are the main limiting factors in selection of particulate materials for use as radioactive tracers.

The larger particles, those used for capillary blockade studies in man, are made from partially denatured HSA (Fig. 4-7). The basic chemistry is to convert the soluble serum protein into an insoluble particulate suspension that can subsequently be readily labeled with a short-lived radionuclide. Heat or chemicals can be used to denature and precipitate the albumin. To make microspheres, the albumin is suspended, by homogenization, in oil. The oil is heated, causing the protein to solidify because of denaturation in a spherical form. Aggregating albumin is a chemical process parallel to cheese making; microspheridizing albumin is a chemical process parallel to french frying (Fig. 4-8).

SOLUBILITY

Most diagnostic tracer tests require a soluble form of the tracer. The solubility must be such that an adequate quantity of the material can exist in a small volume of solution that makes up the injection, and it must likewise remain soluble as it mixes with the fluids in the body. Many substances immediately form a precipitate in the blood; except in the case of sodium phytate, which forms a colloid on injection with the calcium ions in the body to make a liver scanning agent, this is a problem to be dealt with. We are, in general, concerned about solubility in water solution because this is how most of the materials are received and prepared for injection. However, in the body, membrane permeability is promoted by solubility in lipids (fat). The water-soluble agents do not penetrate most biologic membranes easily. It has become necessary to study lipid solubility and to make compounds specifically designed to cross certain membrane barriers. **Emulsions** of water-insoluble materials have been proposed as radiopharmaceuticals that could be distributed as usual by the blood. This concept is discussed

on pp. 73 to 75. Tiny gas bubbles might also be distributed by regular body fluid transport mechanisms.

Molecular size of the tracer determines, to some extent, its biodistribution. Drug molecules with a molecular weight of more than 100 to 200 do not cross the intestinal barrier in general and are not absorbed from the cerebrospinal fluid; materials with molecular weights of less than 300 are passively excreted by the liver into the bile in small amounts; molecules with a molecular weight of less than 30,000 may be filtered through the glomeruli and appear in the urine.

TAGGING REACTIONS

The chemical reactions used to tag molecules or particles with a radionuclide may ultimately influence the biodistribution of the tracer. When proteins are tagged, structural alterations, functional group changes, fragmentation, and polymerization may be side reactions not immediately appreciated. The physical conditions present during ^{99m}Tc tagging reactions undoubtedly affect the kinds, number, and relative abundances of both the **oxidation** and **complex** states of the radiolabeled species. It is to our advantage to develop tagging reactions that produce a single radioactive species in which the bond between the radionuclide and the remainder of the molecule is of the required strength.

One would also like for the chemical synthesis of radiopharmaceutical compounds to occur quickly and under conditions that permit sterile handling and produce a product which can be easily converted to an acceptable pharmaceutical. This means that the chemical and physical form of the material is suitable for intravenous administration and that the other chemicals present are also acceptable in the injectate. The synthesis should occur without too much human manipulation. This helps to keep the radiopharmacist's own radiation exposure to a minimum.

The material, once produced, should be stable for as long as it needs to be; ideally, shelf-life should be determined by the physical half-life, thus minimizing the number of new batches that must be made and tested (Fig. 4-9). The material should be subject to as little **self-radiolysis** as possible and should not be subject
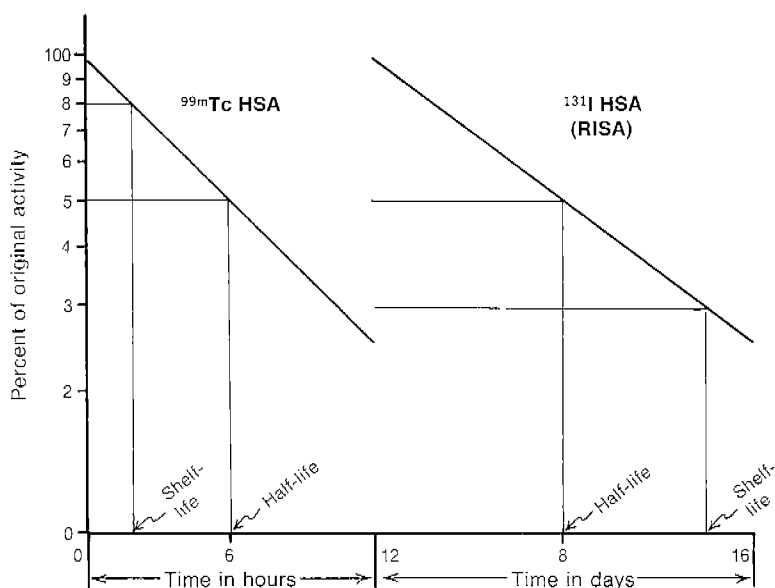
Fig. 4-9. Usually shelf-life is determined by physical half-life. In some cases other factors predominate. For example, ^{99m}Tc HSA usually has shelf-life of about one third the 6-hour half-life of ^{99m}Tc. This is because of in vitro oxidation of the technetium. ^{131}I HSA (radioiodinated serum albumin, or RISA) is generally stable, in vitro, for up to two half-lives of the ^{131}I.

to oxidation or disintegration on exposure to air or to room temperatures. If the material is to perform successfully inside the patient, it must remain stable after injection.

IN VIVO STABILITY

There are many solubility and binding factors that affect the localization and clearance rates and determine whether a particular formulation of a tracer will be useful as a radiopharmaceutical, either for functional studies or for static imaging. For some agents, localization in a particular organ will further depend on factors that control the amount of blood flow to the organ of interest. The myocardial uptake of K^+ and Tl^+ is influenced by the relative amounts of myocardial and liver blood flows. A further consideration is the role of other drugs or blood substances on tracer formulations. Plasma citrate concentrations have not been found to appreciably influence the biodistribution of ^{67}Ga citrate; however, many of the possible influencing factors are yet to be studied.

Once the material has been injected into the body, it may exist as a free substance in the body and blood, or it may tag to red cells or plasma proteins. For example, either hexavalent chromium or pertechnetate in the presence of tin will bind to red cells in vivo. Trivalent indium, when injected at pH 1.5 to 3, binds to transferrin. This is a blood protein with iron binding sites for which the indium competes. Most drugs will be at least partially and reversibly adsorbed onto blood elements. Serum albumin has a great affinity for many species, as does serum globulin.

Once the material is inside the patient, one is more concerned than ever about its characteristics. The ideal aimed for is that the material does its job and then vanishes, either by physical decay or by biologic elimination. There have even been attempts to accelerate elimination by loading secondary sites of localization with competing materials. SSKI solution is given to load the thyroid with iodine, so that as radioiodine is released by metabolism of a radioiodine-tagged molecule, the nuclide will be excreted rather than accumulated in the thyroid (p. 60). One of the best examples in tracer design in which biologic half-life is controlled

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Protocol for prevention of radioiodine uptake into thyroid*

1. *Radiation doses*   *Absorbed radiation dose (rads/μCi)*
   Tissue
   Thyroid
Unblocked	1.30
Blocked	0.02

   COMMENT: Unblocked thyroid receives a 65 × ↑ in absorbed dose when compared to blocked thyroid.

2. *Procedure for blockade of the thyroid*

   Give patient 5 drops of saturated solution of potassium iodide (250 mg) 24 hours prior to the injection of ^{125}I fibrinogen.

   Give 3 drops of saturated solution of potassium iodide (150 mg) two times daily for 10 days following one injection and for 3 weeks after the last injection if repeated injections are given.

   COMMENT: Other iodide preparations such as Lugol's solution are of a weaker concentration and may not adequately block the thyroid.

3. *Patient instruction*

   Saturated solution of potassium iodide (SSKI) requires a prescription for dispensing. Patient directions may read:

   > SIG: 5 drops 1 day prior to injection, then 3 drops twice daily for 10 days, or longer if directed by your physician.

4. *Procurement of SSKI*
   a. The UNM Radiopharmacy can stock your nuclear medicine department with 1-ounce pre-packaged bottles of SSKI for outpatient dispensing if your department desires.
   b. SSKI is available from your hospital pharmacy if a written prescription is presented by your outpatient.
   c. SSKI is available on the ward floors for inpatients; the nuclear medicine physician should ensure that the dosage regiment is entered in the patient's daily medication chart.

   ---
   *Prepared by Robert Adams, R.Ph., for clinics receiving ^{125}I fibrinogen from the University of New Mexico Radiopharmacy.

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is in the use of albumin microspheres. The rate of biodegradation is determined by the amount of heat used to prepare the microspheres. The microspheres are made to optimize their residence time in the lungs. The typical imaging examination takes 1 to 2 hours to ensure that the static images have adequate information density and that all the views have been taken that are required. If the material is to be used for static imaging, the effective half-life should be about 3 hours to permit adequate count rates. (This assumes rapid localization has been achieved at the start of the examination; for more about this, see the following paragraphs.)

The effective half-life is a function of both physical and biologic half-lives.

$$\frac{1}{T_{eff}} = \frac{1}{T_b} + \frac{1}{T_p} \tag{1}$$

or

$$T_{eff} = \frac{T_b T_p}{T_b + T_p} \tag{2}$$

If either the physical or the biologic half-life is very long compared to the other, the effective half-life will be equal to the short one, so a short biologic half-life can substitute for a short physical half-life in removing the material from the body. ^{169}Yb DTPA is an example of the use

Fig. 4-10. Both $^{99m}TcO_4^-$ and ^{99m}Tc DTPA are used for brain scanning. Both have relative advantages and disadvantages. For instance, absolute uptake of $^{99m}TcO_4^-$ is often higher because its blood clearance is slower, but ^{99m}Tc DTPA gives higher contrast, since its blood clearance is faster. Blood clearance determines, in part, optimum time for taking images.

of this principle. It should be pointed out here that if a material containing a nuclide of long physical half-life is quickly released from the imaged organ by virtue of excretion or chemical change, it must not go elsewhere in the body and confer its radiation dose there. The good radiopharmaceuticals actually leave the body when their work is finished. Hydration of bone-scan patients promotes rapid blood clearance and renal excretion of most of the ^{99m}Tc-labeled bone-seeking tracers.

CLEARANCE

Many scanning techniques involve radiopharmaceuticals that require the clearance of material from the background in order to permit viewing of the area in question. This is true of the active-transport and passive-diffusion mechanisms in particular. When the clearance occurs slowly, it obviates the use of short-lived nuclides. After gallium localization in tumors and abscesses, 2 days are required for background clearance; hence neither ^{68}Ga ($T_{\frac{1}{2}} = 68.3$ minutes) nor ^{99m}Tc ($T_{\frac{1}{2}} = 6$ hours) would be suitable for this examination.

Imaging requires contrast. The only way in which we can distinguish a figure against the background is if the tracer localizes to some degree and thereby provides our measuring instruments with a significant target-to-nontarget

ratio. It is better if the target is significantly more radioactive than its surroundings. This is usually expressed in a significantly larger percentage uptake of the administered dose per gram in the target organ relative to surrounding tissues. Animal studies can reveal these ratios before the material is prepared for clinical trial. The optimum time for imaging must also be discovered. This is a function of the target-to-nontarget ratio and of the absolute quantity of radioactivity in the target organ. It is, of course, also possible to image cold spots: areas which do not concentrate radioactive material in the presence of surroundings that have more radioactivity. This is sometimes all we can do. However, our instruments can reveal much more easily small pinpoint-sized, highly radioactive areas than they can small nonradioactive areas. It is the lack of spatial resolution of the instruments that makes it difficult to discern cold areas. In studies designed to select one of several possible tracers, contrast, absolute uptake, and time of optimum visualization are determined for all candidate tracers (Fig. 4-10). The best tracers provide a good combination of all three parameters.

AMOUNT OF TRACER

There are conditions under which we must consider the number of receptor sites for the
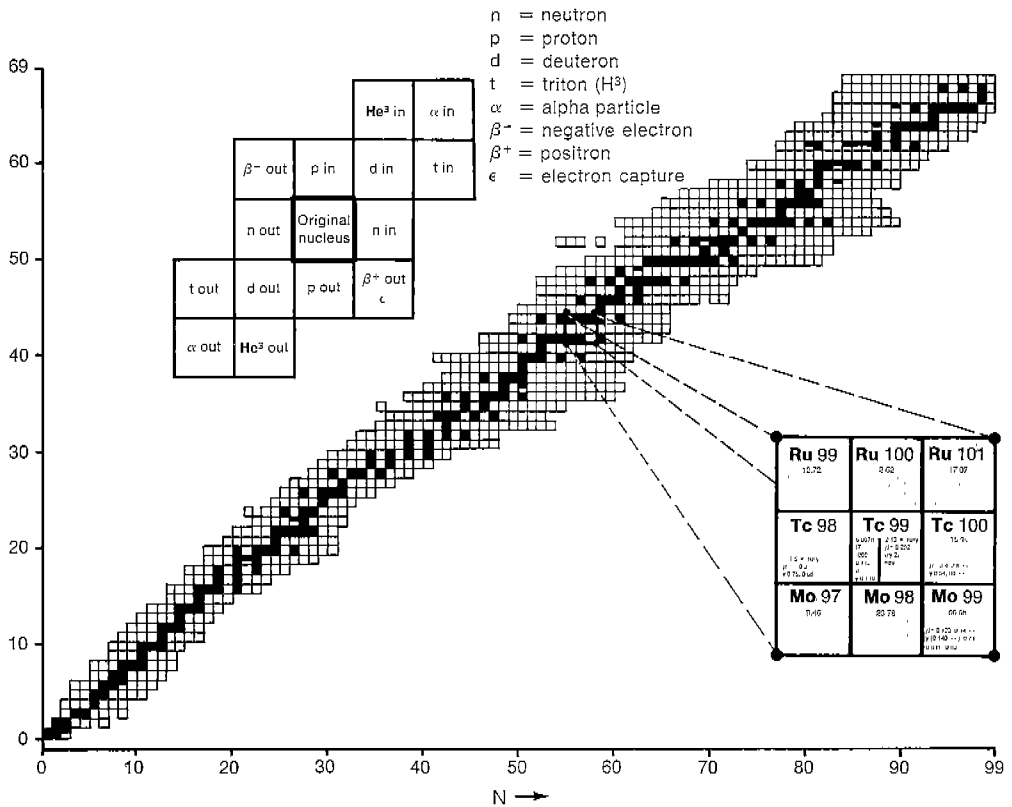
Fig. 4-11. Chart of nuclides (incomplete) showing enlargement of section surrounding ^{99}Tc. Student can refer to large wall charts for detailed information on all known nuclides.

material that we are planning to use diagnostically. In the case of lung-scanning materials, a large safety factor was desired to avoid compromising the patient's circulation. In the case of liver-scanning materials, it is possible to overload the liver with colloid particles. We do not want to come close to this limit unless we are specifically measuring the RE capacity.

If hormone receptor sites are to be studied with radioactive tracers, both the specific activity and the total quantity of tracer may become a very critical issue.

The drug state of the patient may have a great effect on the efficacy of the material being used for scanning. There is a suspicion that the drugs previously administered to the patient affect the quality of a bone scan, for example. Some drugs inhibit the tagging of red cells by ^{51}Cr. If the kidneys are not functioning well, material will not be eliminated, and there may

be a high background that is unacceptable for imaging purposes. Thyroid blocking is one of the most obvious problems. In the study of thyroid disease and its treatment, agents that will block the thyroid, ranging from exogenous iodine through propylthiouracil, must be considered when performing diagnostic tests on the thyroid.

Elements by groups in the periodic chart

We are potentially interested in all nuclides with half-lives from a minute to a year, which are gamma, not alpha, emitters, as potential raw material for making radiopharmaceuticals (Fig. 4-11). When we use the periodic chart together with the chart of the nuclides, we quickly learn that most of the nuclides do not have a suitable gamma ray. In fact, these criteria limit the **elements** under consideration to those with

$$CH_3-S-CH_2-CH_2-CH-COOH \qquad CH_3-{}^{75}Se-CH_2-CH_2-CH-COOH$$

<div style="text-align:center">

NH₂ (under CH of first) ... NH₂ (under CH of second)

</div>

$$\underset{NH_2}{\mid} \qquad\qquad\qquad\qquad \underset{NH_2}{\mid}$$

Methionine   **⁷⁵Se selenomethionine**
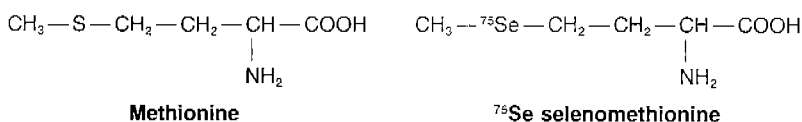
Fig. 4-12. Chemical structures for amino acid methionine and its radiolabeled analog, ⁷⁵Se seleno-methionine.

I⁻   TcO₄⁻   K⁺   Tl⁺
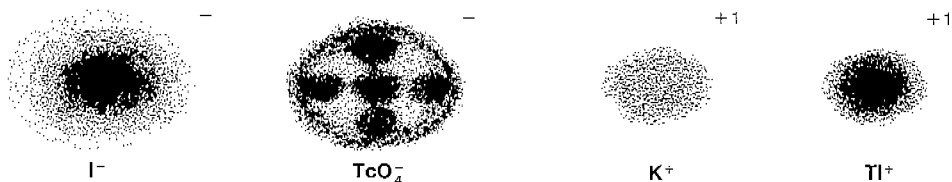
Fig. 4-13. Two examples are analog tracers with similar biodistributions resulting from similar physical chemical characteristics of ionic size and charge. In their initial biodistributions, pertechnetate ions mimic iodide ions, and thallous ions mimic potassium ions.

Fig. 4-14. Simplified version of periodic chart of elements.

atomic numbers between 20 and 83. The positron emitters form a special class so that if they can be considered useful, the list can be extended down to element number 6. The body is 96% hydrogen, carbon, nitrogen, and oxygen. None of the isotopes of these elements have suitable gamma emitters. Some are marginal as positron emitters—marginal because their half-lives are so short. The utility of tracer compounds containing the actual radioactive elements of real-life rather than substitute or added radioactive labels is obvious. However, this is difficult to achieve, and for these four major elements it is only possible with positron-emitting isotopes.

Further analysis shows that calcium, potas-

sium, sodium, magnesium, and iron have gamma-emitting isotopes but that their energies are too high, in general, to be practical for imaging. However, strontium, iodine, molybdenum, zinc, selenium, vanadium, copper, chromium, manganese, and cobalt have gamma-emitting isotopes in a good energy range, although manganese and vanadium are not suitable for human use. These are, of course, not all the suitable nuclides.

Once the possible nuclides have been pointed out, it is chemistry that will enable them to be targeted to a particular location. There are several ways in which a nuclide may be used:

1. As a substitute for a stable isotope in a biologically active molecule or biochemical
2. By itself in a stable chemical form

3. Frankly tagged onto another molecule where it ordinarily does not belong, in the hope that either the body cannot tell the difference or that the tagged species will have some special utility all its own

The first case requires an understanding of the biochemistry so that an important molecule can be selected for radionuclide incorporation. ^{75}Se selenomethionine is an example of this approach. Since no good isotope of sulfur is available, ^{75}Se was substituted for S in one of the essential amino acids, methionine (Fig. 4-12). Amino acids are the starting material for protein synthesis. Thus, a gamma-emitting amino acid was designed as a tracer for sites of protein building, such as occurs in the pancreas during synthesis of the digestive enzymes.

The second case involves studies that reveal
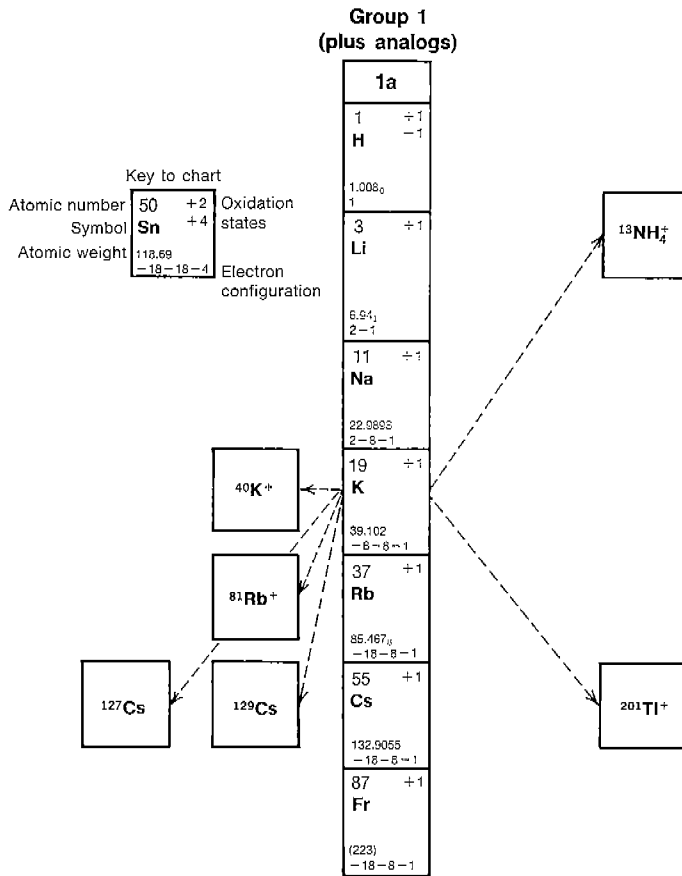
Fig. 4-15. Expansion of periodic chart for alkaline metals. Dashed lines point out analogs used to trace potassium ions in body.

the essential roles of the chemical species in the normal biochemistry or physiology. ^{42}K is an example of this approach. Potassium ions are concentrated within muscle cells; thus radiopotassium or its analog, Tl^+, are natural candidates as radiopharmaceuticals for tracer studies of muscle function (Fig. 4-13).

The third case involves the chemistry of getting the radionuclide tag incorporated into another molecular species as the first goal. As the second goal, we are concerned with having the radionuclide stay in place under the conditions in which the pharmaceutical is handled and those which it will encounter once in the body. The behavior of the tagged material must be studied to see if it duplicates the biodistribution of the untagged material or if it has an interesting and useful biodistribution of its own. It is well to understand the biodistribution of the material being tagged, both in the concentrations in which it may ordinarily be used or found (for example, in an antibiotic) and in the concentrations that will occur when it is tagged. The two biodistributions may be very different. Much grief can be avoided in radiopharmaceutical development if these principles are remembered. As an example, investigators sometimes find that ^{11}C-labeled compounds have a different biodistribution than the same compound labeled with ^{14}C. The difference can be attributed to the fact that it is possible to make ^{11}C compounds of much higher specific activities than is possible for ^{14}C compounds. The total amount of a radiocarbon-labeled tracer that is administered influences its biodistribution.

An examination of the periodic chart (Fig. 4-14) provides a generalization of the kinds of chemistry that must be employed to prepare radioactive tracers from radionuclides representative of the various periodic groupings.

GROUP 1

The elements of Group 1 (Fig. 4-15), the alkali metals, are useful as ions. In fact, the strongly ionized species is the only one normally found in aqueous media. These ions are absorbed from the GI tract, excreted in the urine, and uniformly distributed in most tissues; however, 10% to 50% of certain alkali metal ions are concentrated in skeletal muscle. Potassium

and its analogs are used to visualize the myocardium and to measure lean body mass.

GROUPS 2 AND 3

The elements of Groups 2 and 3 (Fig. 4-16) are bone seekers. Group 2 elements are also highly ionized and are therefore not suited for the preparation of water-soluble compounds other than the simple ionic species. Calcium and strontium isotopes are administered as the soluble salts, usually as a chloride or nitrate. Group 3 elements are less soluble. They usually require an acid solution to assure water solubility, or they may be solubilized at neutral pH by complexing them with substances like citric acid. Gallium is prepared as a citrate solution. Indium is prepared as a dilute (0.05N) hydrochloric acid solution. With Group 3 elements chelation can be used to prepare stable compounds. Indium 111 and 113m form extremely stable chelates with DTPA (diethylenetriamine pentaacetic acid).

Groups 2 and 3

2	3
4 ÷2 Be 9.01218 2 2	5 ⊦3 B 10.81 2−3
12 ⊹2 Mg 24.305 2 8 2	13 +3 Al 27.9815 2−8−3
20 +2 Ca 40.08 −8−8−2	31 +3 Ga 69.72 −8−18−3
38 ÷2 Sr 87.62 −18 8−2	49 ⊦3 In 114.82 −18−18−3
56 +2 Ba 137.34 −18−8−2	81 +1 Tl +3 204.37 32 18 −3
88 ÷2 Ra (226) −18−8−2	

Fig. 4-16. Expansion of periodic chart showing alkaline earth metals and aluminum groups.

Groups 4, 5, and 6

4	5	6
6 +2 C +4 −4 12.011 2−4	7 +1 N +2 +3 +4 +5 −1 14.0067 −2 2−5 −3	8 −2 O 15.9994 2−6
14 +2 Si +4 −4 28.086 2−8−4	15 +3 P +5 −3 30.9738 2−8−5	16 +4 S +6 +2 32.06 2−8−6
32 +2 Ge +4 72.59 8−18−4	33 +3 As +5 −3 74.9216 −8−18−5	34 +4 Se +6 −2 78.96 −8−18−6
50 +2 Sn +4 118.69 −18−18−4	51 +3 Sb +5 −3 121.75 −18−18−5	52 +4 Te +6 −2 127.60 −18−18−6
82 +2 Pb +4 207.2 −32−18−4	83 +3 Bi +5 208.9806 −32−18−5	84 +2 Po +4 (209) −32−18−6

Fig. 4-17. Portion of periodic chart headed by carbon, nitrogen, and oxygen, primary structural elements of organic molecules.

GROUPS 4 TO 6

Groups 4 to 6 (Fig. 4-17), which begin with carbon, nitrogen and oxygen, respectively, the backbone elements of organic chemistry, have, most unfortunately, not yielded any tracers of much practical use for nuclear imaging studies. Carbon 11, nitrogen 13, and oxygen 15 all have potential but require a cyclotron and a positron camera together with methods for ultrafast chemistry and radiopharmaceutical preparation. Carbon 14 has been a most valuable tracer for experimental studies. Its use in man is limited to studies in which the samples taken for analysis can be obtained from patients. Breath, urine, and blood are about all of the available ways of sampling biodistribution.

ESSENTIAL TRACE ELEMENTS AND NONESSENTIAL TRANSITION METALS

Most of the essential trace elements* (Fig. 4-18) and some of the nonessential transition metals (Fig. 4-19) have gamma-emitting isotopes that can be employed as radiopharmaceuticals.

_____

*Sr, I, Mo, Sn, Se, V, Cu, Cr, Mg, and Co.

Transition elements

Group 8

21 +3 Sc 44.9559 −9−9−2	22 +2 Ti +3 +4 47.90 −8−10−2	23 +2 V +3 +4 +5 50.9414 −6−11−2	24 +2 Cr +3 +6 51.996 −6−13−1	25 +2 Mn +3 +4 +7 54.9380 −8−13−2	26 −2 Fe −3 55.047 −8−14−2	27 −2 Co −3 55.9332 2−15−2	28 +2 Ni +3 58.71 −8−16−2	29 +1 Cu +2 63.546 −9−18−1	30 +2 Zn 65.37 −8−18−2
39 +3 Y 88.9059 18−9−2	40 +4 Zr 91.22 18−10−2	41 +3 Nb +5 92.9064 −18−12−1	42 +6 Mo 95.94 −18−13−2	43 +4 Tc +6 +7 98.9002 −18−13−2	44 −3 Ru 101.07 −16−15−1	45 −3 Rh 102.9055 −16−16−1	46 +2 Pd +4 106.4 18−18−0	47 +1 Ag 107.868 −18−18−1	48 +2 Cd 112.40 18−18−2
57 +3 La 138.9055 −18−9−2	72 +4 Hf 178.49 −32−10−2	73 +5 Ta 180.947 −32−11−2	74 +6 W 183.85 −32−12−2	75 +4 Re +6 +7 186.2 −32−13−2	76 −3 Os +4 190.2 −32−14−2	77 +3 Ir −4 192.22 −32−15−2	78 +2 Pt +4 195.09 −32−16−2	79 +1 Au +3 196.9665 −32−18−1	80 +1 Hg +2 200.59 −32−18−2
89 Ac +3 (227) 18−9−2	104 32−10−2	105							

☐ Known to be essential

Fig. 4-18. Transition elements include several essential elements.
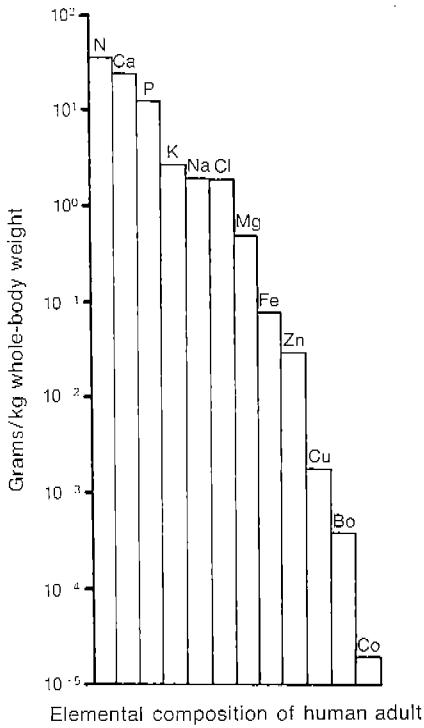
Fig. 4-19. Elemental composition of adult human showing elements other than hydrogen, carbon, and oxygen, which make up bulk of tissues. For example, average adult tissue is 720 grams of water per kilogram. (Based on data from Diem, K., and Lentner, C., editors: Geigy scientific tables, ed. 7, New York, 1970, Geigy Pharmaceuticals [Division of CIBA-Geigy Corp.].)

Most of these elements are found in the lower center of the periodic chart. They can be chelated or complexed into many forms whose behavior is then determined by the characteristics of the complex molecule. Some of the metals actually occur at the active center of some biochemicals: iron in the heme of the red blood cell, cobalt in the center of vitamin B_{12} (Fig. 4-20). The potential uses of these natural compounds have not been fully explored. Some elements can be inserted into materials as substitutes for the naturally occurring elements, such as selenium, which has been used in place of sulfur in methionine. Indium can sometimes be made to substitute for iron or cobalt. Mercury binds very firmly to sulfur under many circumstances and can be used as a tracer or locater for sulfur-containing species.

Chromium 51 has had much utility as a medically useful tracer. As the chromate ion, radiochromium is soluble in aqueous solution. The chromate ion is easily reduced; in fact, RBCs can accomplish the reduction. When reduced to the chromic (Cr^{+3}) redox state, radiochromium is not soluble in pH neutral aqueous solution. Fortunately, the chromic species readily forms complexes or chelates. Thus, chromic ions form relatively stable bonds with erythrocytes, leukocytes, platelets, and proteins, as well as
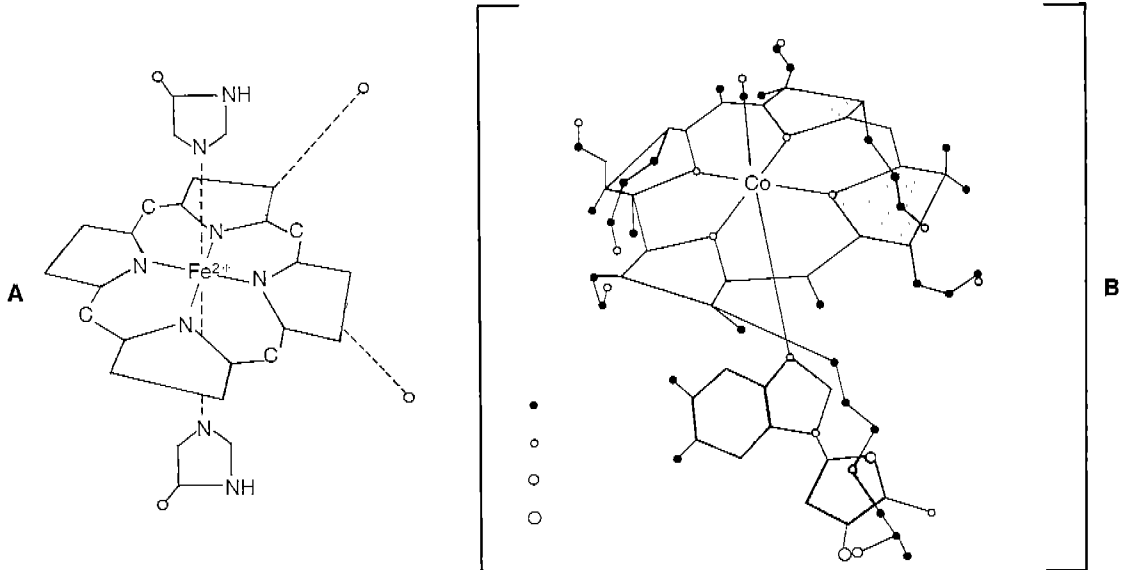
Fig. 4-20. A, Iron is found in body in center of heme, a porphyrin that resides in tertiary structure of hemoglobin. B, Cobalt is found in center of vitamin B_{12}.

**Group 7
Halogens
and iodine
analogs**

	9 F −1 18.9948 2−7	
	17 Cl +1 +5 +7 −1 35.453 2−0−7	
ClO₄⁻	35 Br +1 +5 −1 79.904 −8−18−7	⁷⁷Br⁻
123I⁻ 125I⁻	53 I +1 +5 +7 −1 126.9045 −18−18−7	131I⁻ 132I⁻
	85 At (210) 32−18−7	⁹⁹ᵐTcO₄⁻

Fig. 4-21. Group 7, halogens. Dashed lines show common tracer isotopes of iodine and iodine analogs.

with chelates like DTPA. Technetium chemistry parallels in a very general way that of chromium. Pertechnetate is water soluble; when reduced, it loses its water solubility and, like chromium, can form relatively stable bonds to cells, proteins, and chelates. Pertechnetate is not as readily reduced as chromate; for example, RBCs usually cannot accomplish the reduction. Technetium is also more variable with respect to reduction reactions than chromium; when reduced, several redox states are possible, which makes technetium-labeling chemistry much more complex. However, this also means that many possibilities exist for making tracer compounds.

GROUP 7

Group 7 (Fig. 4-21), the **halogens** from fluorine to iodine, are involved in more complicated and varied compounds for the heavier elements.

54	Xe									Xe 124	Xe 125	Xe 126
53	I	I 115	I 116	I 117	I 118	I 119	I 120	I 121	I 122	I 123	I 124	I 125
52	Te	Te 114	Te 115	Te 116	Te 117	Te 118	Te 119	Te 120	Te 121	Te 122	Te 123	Te 124
		60	62		64		66		68		70	72

Fig. 4-22. Expansion of chart of nuclides in region of iodine. There is only one stable isotope, ¹²⁷I, but many radioisotopes can be produced; several have physical properties that make them useful as radioactive tracers.

Fluorine exists as F_2 and F^- and has only a useful positron-emitting isotope, which has been used for bone scanning; the F^- substitutes for OH^- in the hydroxyapatite crystal of the bone mineral matrix. Chlorine has no useful nuclides for our purposes, except perhaps one positron emitter. Bromine has not been much used so far, but has some potential. Iodine, on the other hand, is the grand old element of nuclear medicine, particularly ^{131}I (Fig. 4-22). Of course, ^{125}I is used extensively in in vitro tests, since it has a long shelf-life, though it is not suitable in energy for imaging. ^{123}I, with a 13-hour half-life and a principal gamma-ray energy of 159 kev, is well on its way to becoming a star, if high production costs can be overcome (Fig. 4-23). The popularity of iodine stems in part from its availability since the early days of nuclear medicine. It was used as a physiologic tracer to diagnose thyroid disease and as a radiotherapeutic agent for the treatment of hyperthyroidism and some thyroid cancers. Contrast agents are made to contain iodine because of the electron density of an element of mass 127 and because this element can be incorporated into a variety of organic compounds. Thus, it was natural to prepare these compounds with radioiodine to make a radioactive tracer for use in lieu of an electron-dense dye. Iodine can be readily bound to the amino acid, tyrosine. This amino acid is part of the structure of most proteins; therefore, these proteins can be iodinated and used as a tracer.

Iodinated compounds often have biodistributions which approximate that of the nonlabeled substance which they are designed to trace. In other instances, the iodine changes the behavior of the molecule so drastically that it is not useful. There is also the situation in which the change in biodistribution caused by iodination can be used to advantage. An example of this is the use of highly iodinated radiolabeled fibrinogen. With only one iodine atom per molecule of protein, the behavior of iodofibrinogen is approximately that of native fibrinogen. When more iodine atoms are added per molecule, the clotting function of the molecule remains intact while the biologic half-life in the blood is reduced (Fig. 4-24). This can be used to achieve better target-to-nontarget ratios earlier than when the monoiodinated tracer molecule is used.

GROUP 0: THE NOBLE GASES

Group 0 elements (Fig. 4-25) are the so-called inert gases; however, they are not entirely inert. They form a great many compounds, but most are not stable under physiologic conditions. The inert gases themselves are useful, however. They are very fat soluble and even have anesthetic properties at high concentrations. Thus, the inert gases are widely used to study ventilation of the lungs (Fig. 4-26). They can also be used to study blood perfusion to almost any area of the body. One way to do this is to saturate a fatty area such as the brain by having the patient rebreathe xenon and then measure the xenon washout. Another way of using xenon is to inject it on the arterial side of an organ and monitor the radioactivity of the organ as the xenon washes in and out. The measurements can be used to indicate blood flow. An advantage of the technique is that recirculation of the tracer is minimized. When the xenon

Xe 127	Xe 128	Xe 129	Xe 130	Xe 131	Xe 132	Xe 133	Xe 134	Xe 135	Xe 136	Xe 137	Xe 138	Xe 139	Xe 140	Xe 141
70s 36.4d	1.92	-1.05	4.08	11.08d 21.18	0.8ms 26.89	2.20d 5.27d	20s 10.44	15.7m 9.16h	8.87	3.82m	14.2m	40s	13.6s	1.72s
I 126	I 127	I 128	I 129	I 130	I 131	I 132	I 133	I 134	I 135	I 136	I 137	I 138	I 139	I 140
13.0d	100	25.01m	1.6×10^7y	8.0m 12.4h	8.05d	2.26h	20.8h	52.0m	6.7h	85s	22.3s	6.0s	2.0s	1.5s
Te 125	Te 126													
58d 6.99	18.71													

| 74 | 76 | 78 | 80 | 82 | 84 | 86 |

reaches the lungs in the blood, about 90% of it is exhausted into the air. Since recirculation is not significant, the examination can be repeated at short time intervals. To prepare a radioxenon or other noble gas isotope for injection, the gas is solubilized in saline. The gas is introduced under pressure to get it into the saline. The handling of these solutions is difficult because the noble gas rapidly leaves the aqueous phase if the solution is exposed to air.

HEAVY METALS AND RARE EARTHS

At the bottom of the periodic table a number of elements are found that have isotopes with attractive physical decay characteristics. Gold 198 has been used as a colloid. Mercury 196 and 203 are used as organometallic compounds. The two isotopic forms of Hg chlormerodrin (Fig. 4-27) used for kidney imaging are the prime examples. Thallium 201 in the $+1$ redox state is used as a potassium analog for myocardial imaging. Lead 203 can be used as a red cell label. Many organometallic lead compounds

Iodine 123
Electron capture decay

Fig. 4-23. Decay scheme of ^{123}I.
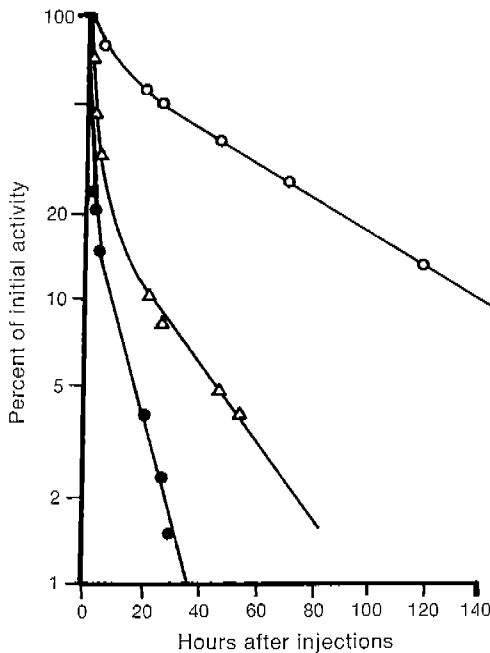
Fig. 4-24. Blood clearance of radioiodinated fibrinogen showing increased clearance with increasing numbers of iodine atoms per molecule of protein: *open circles,* 0.5 iodine atoms per molecule; *triangle,* 50 iodine atoms per molecule; *closed circles,* 100 iodine atoms per molecule. (Based on data from Harwig, J. F., Coleman, R. E., Harwig, S. S., et al.: J. Nucl. Med. **16:**756-763, 1975.)

Group 0

Fig. 4-25. Group 0, or noble gases.

have been synthesized, but these remain unexplored as radioactive tracers. Bismuth 203 was once used for brain scanning. Ytterbium 196 is used as a DTPA chelate (Fig. 4-28) for kidney function studies, brain imaging, and cisternography. Platinum complexes have been explored for tumor localization. Rare earth complexes have been explored for bone scanning but are inferior to the currently available ^{99m}Tc complexes. The rare earth colloids have been explored for RE studies but offer no advantage over the ^{99m}Tc colloids in current use.
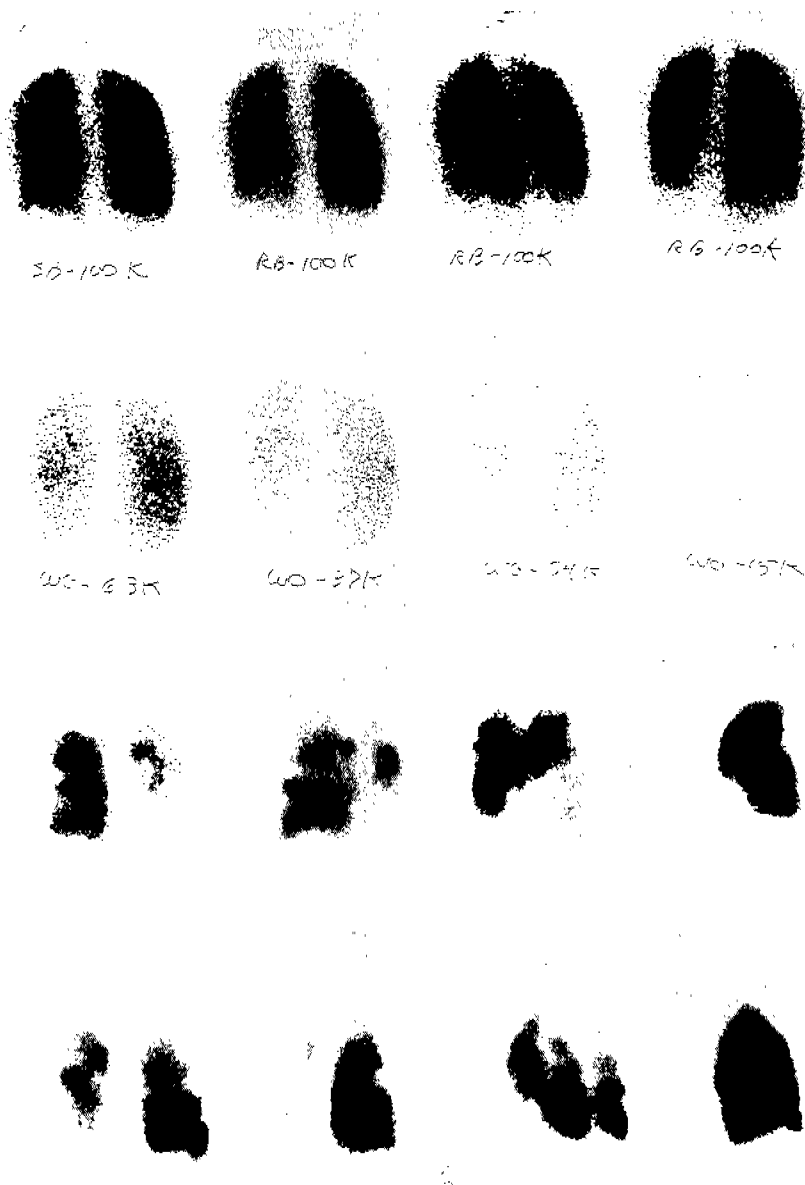
Fig. 4-26. Upper two rows show serial scintigrams of chest during washout phase of xenon 133 ventilation of lung. This patient has normal ventilation. Lower two rows show that this same patient has multiple perfusion defects. Increase in normal ventilation study increases probability that defects seen in perfusion study are due to pulmonary emboli; that is, it rules out chronic obstructive lung disease as cause of perfusion defects. (Courtesy Presbyterian Hospital, Albuquerque, N.M.)
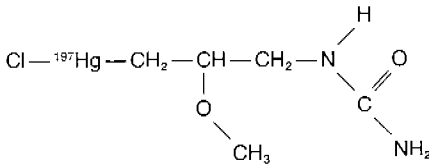
Fig. 4-27. Chemical structure of ^{197}Hg chlormerodrin.

This discussion presents just a glimpse of the usefulness of inorganic and organic chemistry in radiopharmaceutical development. The hybrids—bioinorganic chemistry and medicinal chemistry—are the basic science areas that are keys to the development of new radiopharmaceuticals. Actually, principles from most areas
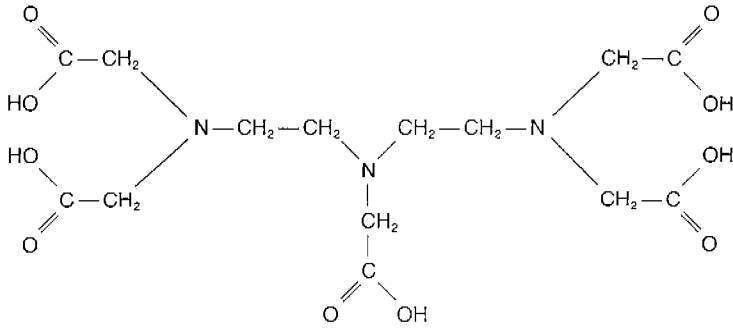
Fig. 4-28. Chemical structure of DTPA, diethylenetriamine pentaacetic acid.
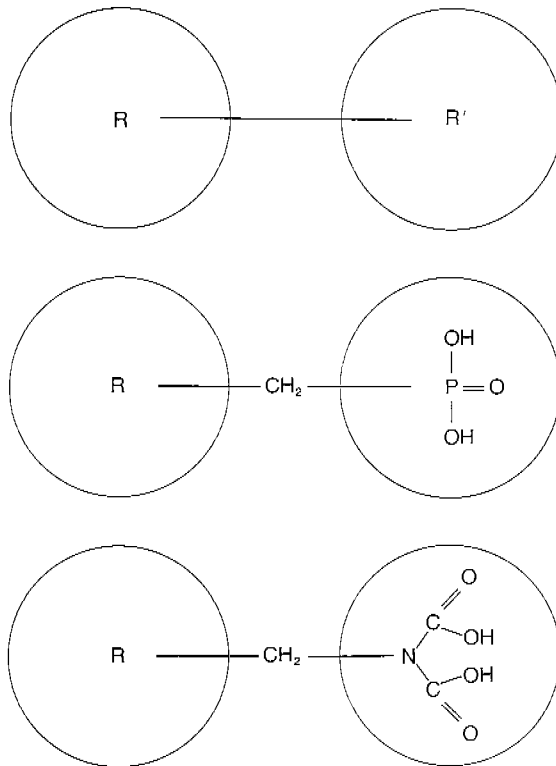
Fig. 4-29. Representation of bifunctional compounds, where *R* gives biologic specificity, and *R'* provides mechanism for labeling compounds with radioactive tracer such as ^{99m}Tc. Middle and lower structures are examples of functional groups designed to bind ^{99m}Tc and other radionuclides.

of chemistry can be used in the search for new tracers.

Bifunctional compounds designed for use as radiopharmaceuticals

Bifunctional compounds are those which are designed to carry out two purposes simultaneously. One purpose is to incorporate a moiety that binds ^{99m}Tc or other radionuclide. The other purpose is to achieve a given biologic specificity (Fig. 4-29). The biologic purpose may be to trace the metabolism of an amino acid. Or the purpose may be to increase fat solubility so that biologic membranes can be penetrated, carrying a ^{99m}Tc tracer across. EHDP (1-hydroxyethylidene-1,1-disodium phosphonate)* binds ^{99m}Tc tightly and can be attached to other chemical groupings. The problem that sometimes occurs is that if the Tc complexing group is too large, its own properties can dominate the behavior of the compound in the body.

It is in this area of development of new radiopharmaceuticals using ^{99m}Tc that the lack of a well-understood chemistry for Tc is felt so deeply. Proteins, drugs, fats, and organic molecules of all kinds are not easily labeled with Tc. Much effort should be put into this topic. Liposomes and vesicles are being evaluated as carriers of radioactivity with the expectation that in this role they may serve as a new class of radiopharmaceuticals. A liposome is a colloidal droplet in which a bimolecular layer of fat and fat-soluble substances surrounds one or more aqueous inner droplets, as diagrammatically illustrated in Fig. 4-30. A liposome may contain several layers of oil and water phases, which give it an onion-like character. A vesicle, the most elemental of liposomes, is composed of simple lipid bilayers that enclose a single aqueous-phase microdroplet. Fig. 4-31 illustrates some reactions of this type of tracer.

At least two general methods exist for tagging these lipid **micelles** with radioactivity. The micelles may be prepared in the presence of

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*Castronovo, F. P., McKusick, L. A., Potsaid, M. S., et al.: The phosphate moiety: labeling with ^{99m}Tc-(Sn) after synthetic attachment to diverse biological compounds. In Subramanian, G., Rhodes, B. A., Cooper, J. F., and Sodd, V. J., editors: Radiopharmaceuticals, New York, 1975, Society of Nuclear Medicine, Inc.
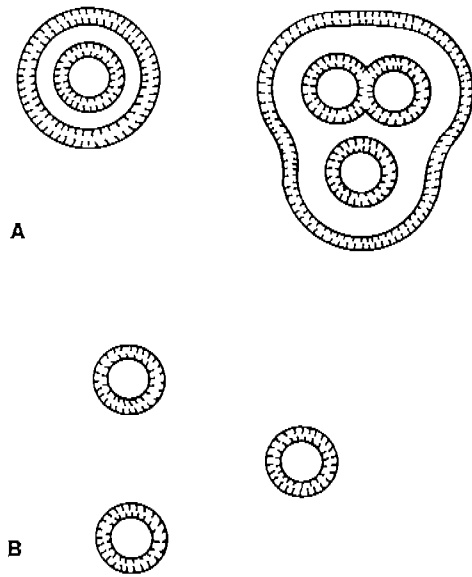
Fig. 4-30. A, Drawings of liposomes showing aqueous-phase droplets and layers enclosed in bimolecular layers of lipid. **B,** Drawings of vesicles showing simple single-droplet structure. (From Rhodes, B. A.: J. Nucl. Med. **17:**1102-1103, 1976.)

a labeled water-soluble substance, such as diethylenetriamine pentaacetic acid tagged with technetium 99m (^{99m}Tc DTPA), and the enclosed aqueous phase will contain the radiolabel.

The radiopharmaceutical design concept is to develop these as bifunctional substances. One end would have a specific biochemical property that would be the functional group of a hormone or hormone receptor, an antibody or antigen, or an enzyme poison. On the other end of the substance would be a site for attaching the radioactive label. Ideally, the two functions, biochemical specificity and radioactive tagging, would not interfere with each other. Fig. 4-32 compares the bifunctional chelates *(A)* to vesicles *(B)*. An advantage of vesicles or liposomes over the chelates is that more than one radioactive atom can be attached to each biochemically specific group; that is, theoretically the specific activity is not limited when vesicles or liposomes are employed as the carrier.

Biochemicals in the body are small in size when compared to cells but very large when compared to simple molecules such as ethanol or phosphates, for example. Very often, how-

Fig. 4-31. A, Agglutination of radiolabeled vesicles containing antigens in membranes that react with circulating antibodies bridging particles. **B,** Lysis of radiolabeled vesicles containing antigens that react with circulating antibodies, causing release of encapsulated water-soluble tracer. (From Rhodes, B. A.: J. Nucl. Med. **17:**1102-1103, 1976.)

ever, a kernel of the large biochemical or a special shape of the electronic cloud on one side is responsible for the behavior of the molecule that we should like to study or imitate. In the center of the heme, which is the center of hemoglobin, the working part of the red blood cell, there is an iron atom surrounded by a **porphyrin** moiety. The iron is oxidized or reduced, depending on whether it is arterial or venous, and provides the oxygen transport mechanism; it is

this iron that can be poisoned when carbon monoxide binds very tightly to it. The function of the hemoglobin can be studied by following iron porphyrin without the complicating shell around it. In nuclear medicine there is a far greater need to be able to mimic the localization of a certain compound by using a simpler compound with a similar electronic cloud on one side so that the receiving template for the complicated material might be fooled into at-
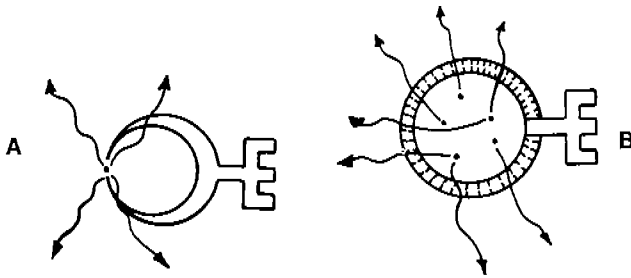
Fig. 4-32. A, Bifunctional chelate showing attachment of radionuclide by a chelation to biochemically specific group. **B,** Same biochemically specific group is attached to vesicle containing radionuclides as solute is enclosed in aqueous-phase droplet. (From Rhodes, B. A.: J. Nucl. Med. **17:** 1102-1103, 1976.)

taching the simpler material. We are using TcO_4^- for I^- in many cases; this substitution provides a reduced radiation dose and improved counting statistics rather than simplicity of the labeled compound. The argument here really is that one need not have the whole of the natural biochemical or other desired compound but only its essence in order to determine function in the system under study. If the active part of the molecule can be discovered, it may be possible to steer clear of this part when it is labeled with ⁹⁹ᵐTc or some other radioactive nuclide; this may even mean covering the active site to chemically protect it and then uncovering it afterward. This is a fairly common trick of the synthetic organic chemists.

Up to the present, much emphasis has been placed on the development of radiopharmaceuticals for use as static imaging agents of internal organs. Now that this approach has been developed, efforts are being directed toward the development of tracers for the in vivo analysis of biochemistry and physiology. Many of the specific biochemical mechanisms have not been explored in terms of searching for new radiopharmaceuticals. These reactions include those of hormones and their receptors, enzymes and their poisons, co-enzymes, antigens and antibodies, opsins, potent drugs like LSD, and vitamins. We can anticipate that the utility of the tracer technique in medical diagnosis will be greatly improved when we are able to design radiopharmaceuticals that will allow for the study of these vital reactions.

Suggested readings

Adelstein, S. J.: The risk:benefit ratio in nuclear medicine, Hosp. Prac. **8:**141-149, 1973.

Bender, M. A.: Letter from the president, J. Nucl. Med. **9:**43-44, 1968.

Counsell, R. E., and Ice, R. D.: The design of organ-imaging radiopharmaceuticals. In Ariens, E. J., editor: Drug design, vol. 6, New York, 1975, Academic Press, Inc.

McAfee, J. G.: Radioactive diagnostic agents: current problems and limitations. In Subramanian, G., Rhodes, B. A., Cooper, J. F., and Sodd, V. J., editors: Radiopharmaceuticals, New York, 1975, Society of Nuclear Medicine, Inc.

Rhodes, B. A.: Liposomes and vesicles: a new class of radiopharmaceuticals, J. Nucl. Med. **17:**1102-1103, 1976.

Wagner, H. N., Jr., and Emmons, H.: Characteristics of an ideal radiopharmaceutical. In Andrews, G. A., Knisely, K. M., and Wagner, H. N., Jr., editors: Radioactive pharmaceuticals, CONF-651111, National Technical Information Service, Springfield, Va., 1966, U.S. Department of Commerce.

Making radiopharmaceuticals safe and effective

Once the basic design of a radiopharmaceutical is accepted, it becomes necessary to establish a fixed procedure for its formulation. Next it is necessary to conduct a series of tests to establish the safety and efficacy of this particular formulation. Since the radioactive species will be administered in tracer amounts (i.e., vanishingly small quantities), it, in and of itself, is not likely to be toxic. Brucer pointed this out emphatically in his vignette entitled "Radiopharmaceuticals Have No Pharmacology."

A good example of the lack of toxicity of a radioactive tracer is the study of the toxicity of ^{113m}In. The element indium is one of the most toxic elements, requiring only 247 μg to cause death in 50% of 20-gram mice. Yet, the amount we use in a human tracer study is only about 10^{-4} μg, which is 10^{-7} below the LD_0 in mice. (The LD_0 is the maximum amount that can be given and still not cause any deaths.)

If **toxicity** is associated with a tracer, it most likely will arise from other chemicals used to formulate it into a preparation that can be administered to patients. Thus, tagging reagents, stabilizers, buffers, suspending or surface-wetting agents, bacteriostatic additives, and impurities are the major ingredients of concern in toxicity studies.

The problem that is usually of more concern is radiopharmaceutical effectiveness. Is the biodistribution predictable and reproducible? Radiopharmaceuticals without a reliable biodistribution can lead to erroneous diagnosis and expensive errors in patient management. Herein lies the major risk associated with the use of radiopharmaceuticals! Even when a radiopharmaceutical failure is recognized prior to making a diagnostic decision, the problems of delay in information, unnecessary radiation exposure, and the expense of an abortive study are still considerable.

Preliminary biodistribution studies

During the development of the formulation, biodistribution studies are usually carried out to establish the in vivo stability of the tracer compound. A prospective formulation for a bone scanning agent may be administered to a group of three to six mice. At 30 minutes postinjection, the mice will be killed and the percentage of the administered dose determined in the femurs, blood, liver, kidneys, spleen, stomach, lungs, and muscle (Fig. 5-1). If the formulation is a good one, the femurs will have a higher uptake of the tracer than the other tissues. For ^{99m}Tc-labeled tracers, each of the organs is an indicator of chemical problems or of in vivo instabilities. These organ uptakes are outlined in Table 5-1.

Animal distribution studies are also often used to determine the stability or the shelf-life of the formulation. Staum and Stern* recommend that studies be done on reagent kits for preparing ^{99m}Tc tracers as a function of time and storage conditions. These data are used to establish the shelf-life of the reagent kits. Bio-

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*Staum, M., and Stern, H. S.: Stability testing. In Rhodes, B. A., editor: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.
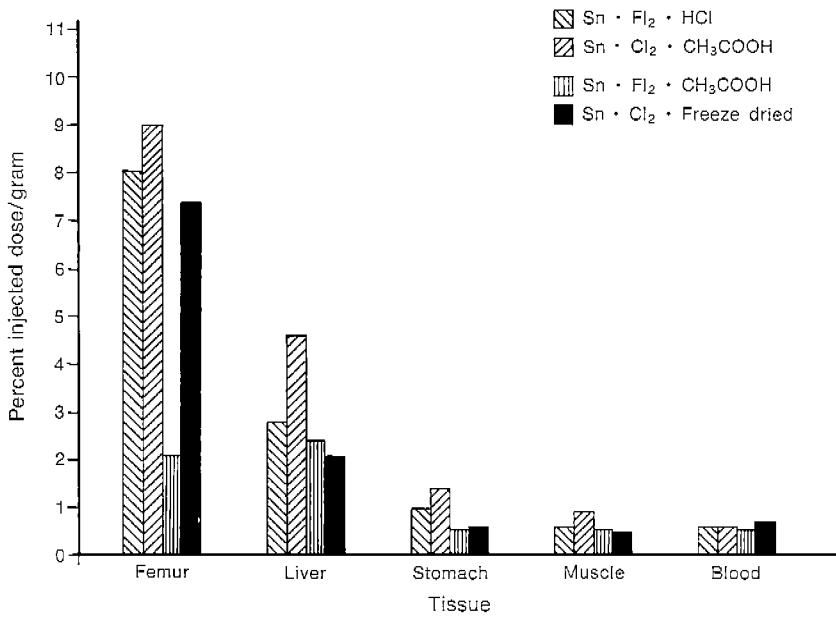
Fig. 5-1. Histogram reporting biodistribution of four different formulations of ^{99m}Tc pyrophosphate in mice.

Table 5-1. Use of organ uptakes to troubleshoot a ^{99m}Tc formulation

Organ of high uptake	Problem indicated
Stomach and thyroid	Free TcO_4^-, incomplete tagging or oxidation
Liver	Insoluble Tc: hydrolysis of reduced Tc or precipitation of labeled compound
Spleen	Tc being bound to blood cells
Blood	Tracer fails to clear from blood; suspect protein binding of tracer or ligand exchange of Tc onto serum proteins
Lungs	Large particle information usually due to precipitation of some ingredient or contamination of reagents with foreign particles
Muscle	Failure of tracer to localize, perhaps due to in vivo ligand exchange of Tc onto cellular structures or cellular metabolism of basic compound leaving reduced Tc to become hydrolyzed and precipitate within tissues

distributions are also performed on the freshly prepared radiopharmaceutical and on the radiopharmaceutical after it has undergone at least one half-life of decay (Fig. 5-2). The results of these biodistributions are used to obtain a first estimate of the expiration period of the tagged product.

Checking system for sterility and apyrogenicity

During the design phase, the designer keeps in mind that the system for preparing the radiopharmaceutical must provide a formulation that is both **sterile** and **pyrogen** free. Thus, the equipment must be amenable to depyrogenation (heating at 200° C for 2 hours), or it must be available as disposable, pyrogen-free equipment such as that used in hospitals. Also, the reagents must be pyrogen free or filtered to remove pyrogens. Alumina columns remove pyrogens, but they also remove or alter many chemicals. The final product must either be sterilized or sterile reagents must be employed throughout and all manipulations carried out in a sterile environment, which is usually a com-

SnF$_2$ · HCl   SnCl$_2$ · CH$_3$COOH   SnF$_2$ · CH$_3$COOH
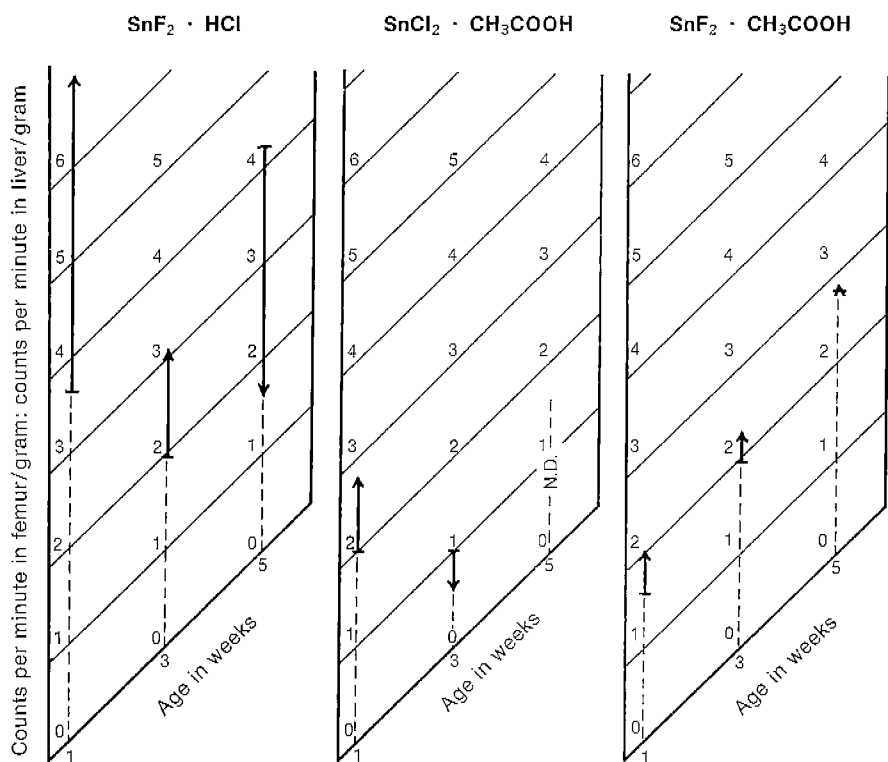
Fig. 5-2. Ratios of ^{99m}Tc pyrophosphate in femur to liver as function of age of reagents. Measurements were made on freshly compounded material and on material 6 hours after compounding. Horizontal line is mean value for ratio for freshly compounded tracer; arrow gives value for ratio 6 hours after compounding. Direction of the arrow, if upward, indicates that material improves with time after compounding or, if downward, that material degrades with time (hydrolysis increases insoluble ^{99m}Tc, which increases liver uptake and thus lowers ratio). Data are reported for three different formulations.

pletely closed system or a laminar flow hood (Fig. 5-3). The preparations are preferably carried out in a "clean room."

STERILIZATION

Many radiopharmaceuticals are not stable under heat or gas sterilizing conditions. The most common method used is to filter the solution through sterile 0.22 μ filters (Millipore filters, for example). At the conclusion of the filtration, the filter is checked to assure that it is still intact. The filter resists the passage of air if it is still in good working order. For most reagent kits, the solutions are prepared with sterile water for injection, U.S.P., and the highest purity chemicals that are available. The chemicals are from control lots and are kept separated from regular laboratory reagents. The final solutions, after sterilization by filtration, are aseptically transferred and aliquoted into vials for freeze drying. Finally, the vials are sealed and labeled.

Some proteins, especially fibrinogen and enzymatically active substances, can be altered by filtration through 0.22 μ filters. Thus, preparations that contain proteins or other delicate molecules require special consideration to assure sterility without degradation of their biologic activity.

STERILITY TESTING

Samples from each lot of reagent kits are tested for sterility, using either U.S.P. methods or radiometric methods. The U.S.P. methods
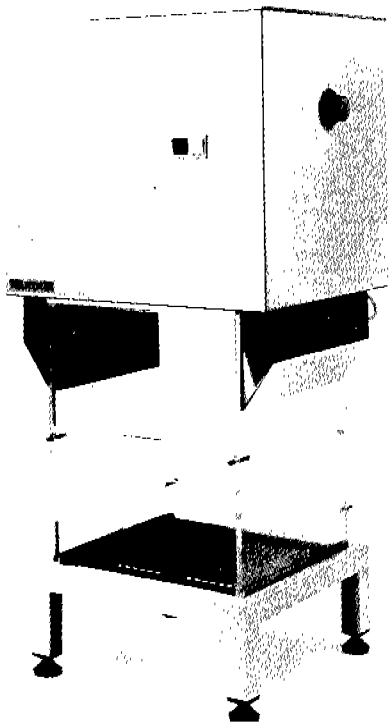
Fig. 5-3. Example of laminar flow hood. (From Rhodes, B. A., editor: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.)

involve the inoculation of growth media and the periodic checking of the tubes while storing them under conditions suitable for growth of biologic contaminants. Fluid thioglycolate at 30° to 35° C is used to test for facultative **aerobic** and anaerobic bacteria. Soybean-casein digest medium is for testing for fungi, molds, and aerobic and facultative anaerobic bacteria. The tubes are kept under observation for 14 days, and any growth is noted (Fig. 5-4). The microorganism should be identified in order to find its source. Obviously, this method is slow and requires culture equipment and experienced personnel. One must be aware of the radiation hazard of the materials being tested.

The radiometric methods involve the inoculation of vials of a medium conducive to bacterial growth that also contain ^{14}C glucose. As bacterial metabolism progresses, $^{14}CO_2$ is emitted. The test vial is sampled at intervals by one of several methods. The $^{14}CO_2$ may be absorbed onto KOH-soaked filter paper and counted in a liquid scintillation counter. An impregnated filter paper may be included in the liquid of the vial, which absorbs the $^{14}CO_2$. Since it is also impregnated with scintillation fluor, it too may be counted in a liquid scintillation counter. The $^{14}CO_2$ may be flushed from the vial and counted in an ionization chamber (Fig. 5-5). Some of these systems have been automated and made up for compact operation commercially. They have the advantage that growth can usually be detected within 24 hours. The disadvantages are that some few bacteria may not emit CO_2 and that high radioactivity may interfere with counting unless the chamber is well shielded.

PYROGENS AND THE PYROGEN RESPONSE

Most pyrogens are heat-stable, filterable, soluble substances that exist as a result of contamination by bacteria, viruses, yeasts, molds, or occasionally chemicals. The usual pyrogens are the products of gram-negative bacterial cell walls, so-called endotoxins, which are primarily polysaccharides. These substances, on injection, cause the body to release other substances that in turn cause fever (Fig. 5-6), chills, malaise, joint pain, leukopenia, and a host of other ill-defined complaints. The symptoms subside within a day, but not without alarming the patient and physicians.

Of course, a pyrogen is defined as any substance that causes a fever with the preceding symptoms and course. Materials other than endotoxins can do this, such as chemicals. It is for this reason that the rabbit test for pyrogens is valuable because it simulates the action of the material in man.

PYROGEN TESTING

Three randomly selected reagent kits from each lot are reconstituted with 1 ml of sterile saline, or an appropriate buffer, and tested for pyrogens. If the rabbit test is employed, the entire contents of one vial is injected into one rabbit. Thus, three vials and three rabbits are used for the rabbit test. The rabbit test is the U.S.P. test for pyrogens.

Briefly, the method is as follows. Mature, healthy rabbits, individually housed under sta-
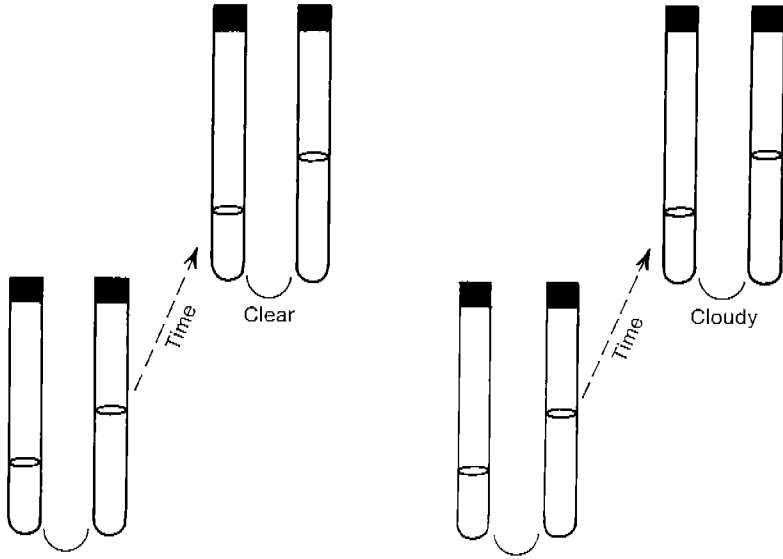
Fig. 5-4. Sterile media, conducive to growth of microorganisms, are inoculated with samples of radiopharmaceuticals. If after incubation samples remain clear, sterility is indicated. Cloudy appearance usually indicates growth. (A few materials can form chemical precipitates in media to give false-positive test results.)
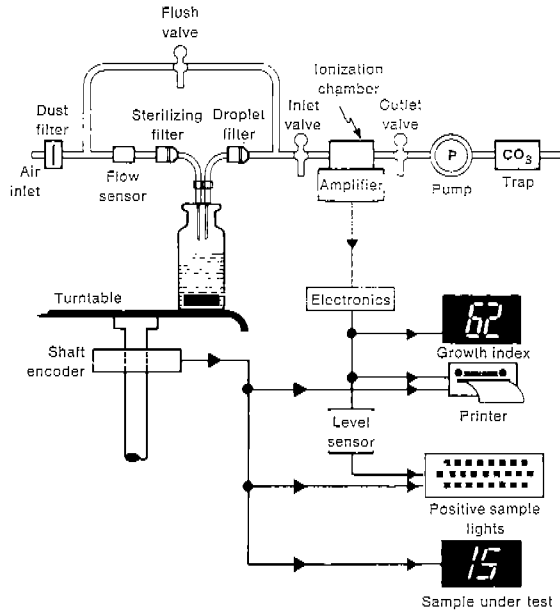
Fig. 5-5. Schematic for detection of bacterial growth by monitoring release of $^{14}CO_2$ from growth media. (From Hetzel, K. R., and Ice, R. D.: Sterilization and sterility testing. In Rhodes, B. A., editor: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.)
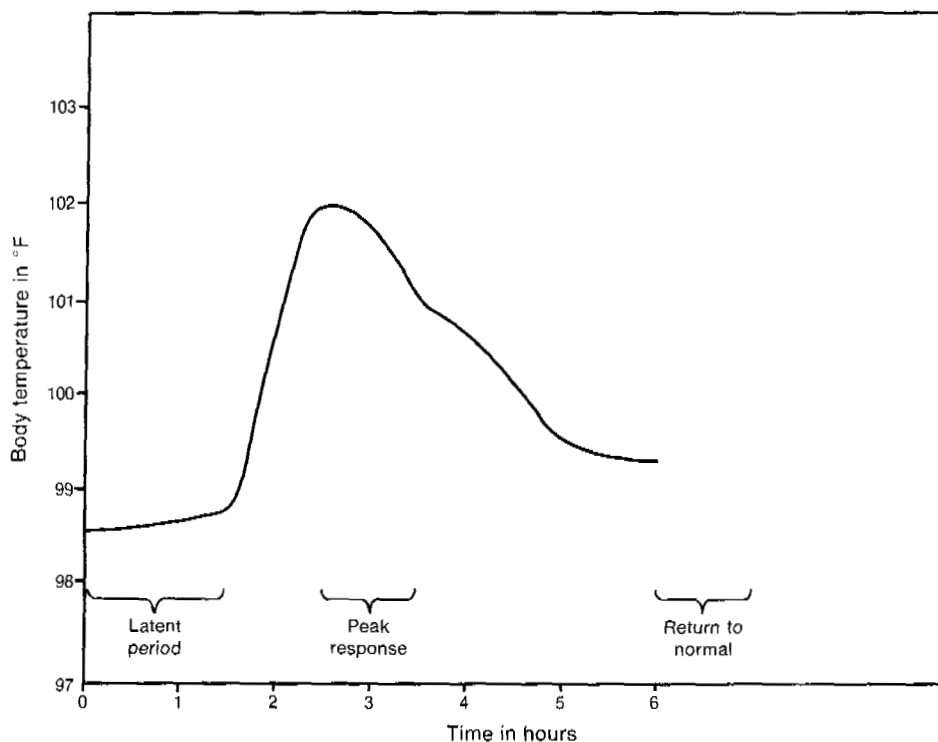
Fig. 5-6. Idealized graph of body temperature of human subject given intravenous administration of drug containing pyrogen.

ble, nondisturbing circumstances and according to FDA rules for animal care, are put into restraint in rabbit boxes, with rectal thermometers in place. The temperatures are usually automatically recorded. Rabbits are used whose temperatures do not vary more than 1° C from each other and are less than 39.8° C. The dose is injected into the ear vein, and the temperature monitored. If no rabbit shows a rise of 0.6° C or more, and if the sum of the temperature rises of the three animals used does not exceed 1.4° C, the material is acceptable. If the material is borderline pyrogenic, it may be tested in five more rabbits, and the results for all eight rabbits pooled. If not more than three of the eight have temperature rises of 0.6° C or more and the sum of all eight temperature rises does not exceed 3.7° C, then the material is acceptable by U.S.P. criteria. Rabbits are used for the pyrogen test because they are extremely sensitive. They must be housed very carefully. Good records of their individual performances must be maintained. They must not

be used too often and must be allowed to rest after a pyrogen reaction. At the start of its use, the rabbit must be trained to accept the restraint, the thermometer, and the injection without becoming so excited that its temperature goes up simply in response to fright. The animals must be challenged with known pyrogens periodically to prove that they are sensitive.

Usually the Limulus (horseshoe crab) amoebocyte lysate gelation test is preferred for the pyrogen testing of radiopharmaceuticals and reagent kits because (1) it is more sensitive; (2) it is faster; (3) it requires smaller amounts of test material; (4) both positive and negative controls can be performed along with each test; (5) it does not generate radioactive rabbits, so it is preferred from a radiologic safety point of view; and (6) it is less expensive and easier to keep (Fig. 5-7).

To test kits, 0.1 ml from each of the three vials used for sterility testing is tested with Limulus lysate (Table 5-2). For the negative

Rabbit test

Limulus test
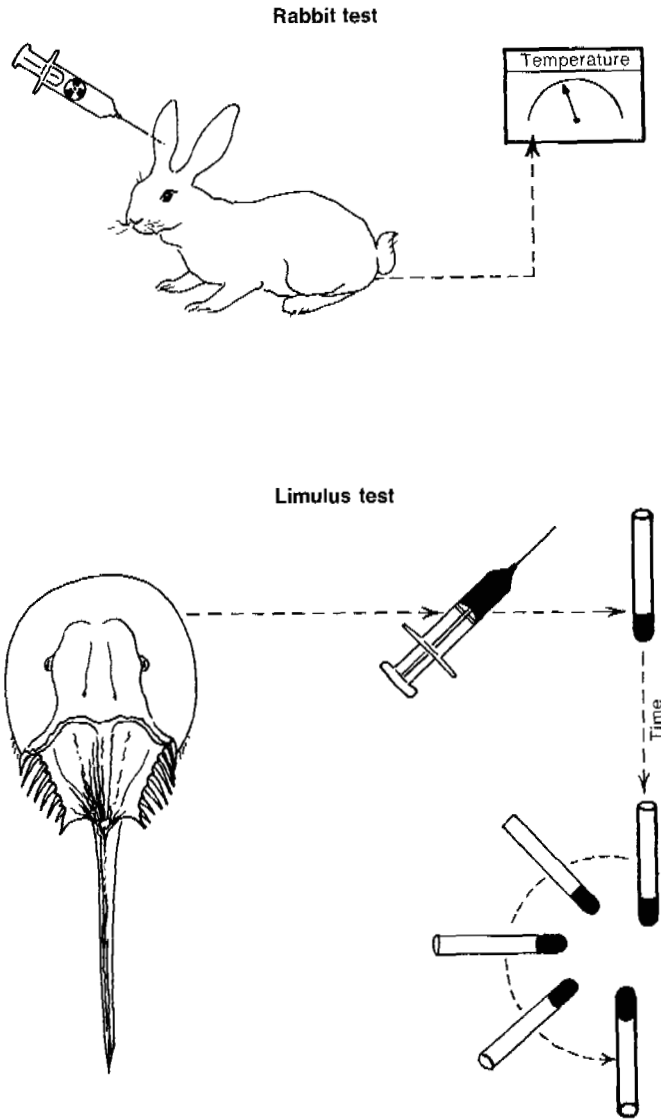
Fig. 5-7. Pyrogen testing employs either rabbits or amoebocytes obtained from blood of horseshoe crab. In first test, end point is rise in body temperature. In second test, end point is gelation of lysate of amoebocytes.

control, a sample of the solution used to dissolve the reagents is simultaneously tested. For the positive control, a test solution containing a known pyrogen is mixed with the dissolved reagents or the radiopharmaceutical and tested to assure that the reagents or the radiopharmaceutical does not inhibit the gelation reactions. A sample of water for injection and water for injection plus endotoxin may be used as controls to ensure that the gelation reaction is occurring correctly. The most common inhibitor is pH outside the range of 6 to 8. If the kit reagents are acidic or basic when dissolved in saline, an appropriate buffer is substituted for the dissolution step. The buffer is then used for the negative control. Alternatively, a portion of the sample to be tested may be brought to the proper pH range with NaOH or HCl. This must be done aseptically to avoid pyrogen contamination.

Table 5-2. Schema of all ingredients necessary for pyrogen test using Limulus amoebocyte lysate and providing for three types of controls

	Negative control	Positive control	Positive Internal control	Test
Lysate	0.1 ml	0.1 ml	0.1 ml	0.1 ml
Test sample	—	—	0.05 ml	0.1 ml
Endotoxin				
Double concentration	—	—	0.05 ml	—
Regular concentration	—	0.1 ml	—	—
Saline	0.1 ml	—	—	—
Total volume	0.2 ml	0.2 ml	0.2 ml	0.2 ml
Results	Should be negative	Should be positive	Should be positive	May be positive or negative

Table 5-3. Comparison of standard and newer methods for sterility and pyrogen testing of radiopharmaceuticals

Test	Standard methods, U.S.P.	Newer methods, non-U.S.P.
Sterility	*Method:* Fluid thioglycolate medium, soybean-casein digest medium *Advantages:* Sensitive *Disadvantages:* Slow	*Method:* $^{14}CO_2$ from ^{14}C glucose in culture medium *Advantages:* Fast, sensitive *Disadvantages:* Automatic methods may have background problems; some kinds of bacteria may not give off CO_2
Pyrogen	*Method:* Rabbit test *Advantages:* Should find all pyrogens *Disadvantages:* Not sensitive enough for intrathecally injected materials, slow, expensive to keep rabbit colony; rabbits may give false-positive and false negative results	*Method:* Limulus lysate test *Advantages:* Sensitive to endotoxin pyrogens, fast, convenient to store and use, more amenable to quantitation of pyrogen, good radiation safety; controls to detect false-negatives and false-positives included as part of routine test *Disadvantages:* May not detect all materials that cause fever; some radiopharmaceuticals inhibit reaction

In the standard Limulus lysate test, 0.1 ml of the lysate is added to 0.1 ml of properly buffered sample. The known pyrogen substance, usually from *Klebsiella* microorganisms or *E. coli,* is added to the selected samples. The samples are observed for 15 minutes to 1 hour. The positive samples should gel, so that the liquid will not run when the tubes are upended. The test may be inhibited by incorrect pH, high salt concentrations, or enzymatic reactions, as well as by some solvents. High levels of albumin may absorb the endotoxin and detoxify it. The Limulus lysate test should soon be recognized by the U.S.P. for testing certain ma-

terials.* It is already in use by researchers for in-process testing of materials and by the manufacturers of radiopharmaceuticals for cisternography because of the extreme sensitivity of the central nervous system to pyrogens. Table 5-3 summarizes the comparison of the older and newer tests for sterility and pyrogens.

Toxicity studies

After a formulation is fixed, that is, the manufacturing instructions are set, formal toxicity studies may be initiated. The objectives of these

*Approved for biologics.

studies are (1) to approximately establish a safety factor and (2) to determine what might be the expected reaction to an overdose.

One indication of the margin of safety of a radiopharmaceutical is the ratio of the TD_{50} dose (the dose that produces toxicity in 50 out of 100 cases) to the usual diagnostic dose. In very large doses, the toxic manifestations may be due to the chemicals, physical properties, or radiation; thus, when talking about margins of safety for radiopharmaceuticals, it is necessary to state the type of toxicity to which one is referring. The toxic effect of lung scanning agents is due to pulmonary hypertension induced by injecting so many particles that a resistance to blood flow through the capillaries of the lungs is increased. This is one type of physical effect. In many cases, to induce a toxic effect from a radiopharmaceutical, such a large volume of the material would have to be administered that the volume itself would become the source of toxicity. This is another type of physical effect.

Two methods are useful in the determination of the LD_{50} (the dose that causes death in 50 out of 100 cases). One is the up-and-down sensitivity test. In this test, the suspected toxic dose is administered to a test animal. If this first animal lives, the next animal is given an incrementally higher dose. If the first animal dies, then the next animal is given an incrementally lower dose. A small series of animals is tested one after the other; in each case, the reaction in the last animal determines whether the next animal receives a higher or lower dose. This is an efficient way to measure the LD_{50} with precision, providing, of course, that the toxic response is immediate. The test can be used to demonstrate the toxic dose of lung scanning particles in mice. When overdosed, the mice die within 5 minutes after the injection. Thus, to carry out this test one mouse is injected every 5 minutes; the result of the test is the LD_{50} at 5 minutes in mice. It is reported in terms of milligrams of particles per gram of mouse. Using this method it was found that iron hydroxide particles are more toxic to the mouse than albumin, either as aggregates or as microspheres. The up-and-down sensitivity test is difficult if the onset of symptoms is delayed.
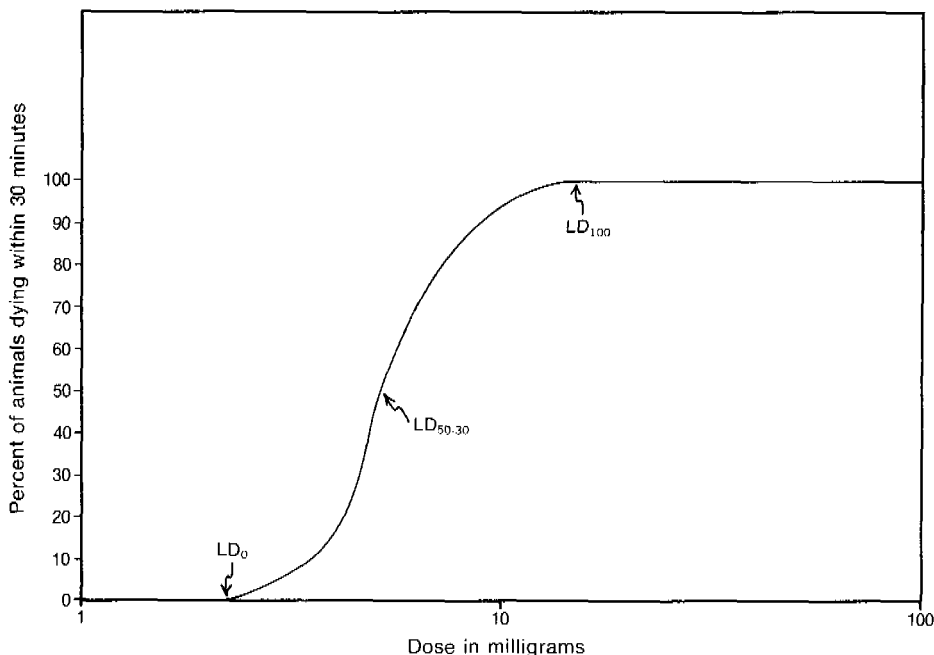
Fig. 5-8. Idealized dose-response curve used to define toxicity of drug. LD_0 is highest dose that causes no deaths. $LD_{50\text{-}30}$ is dose that causes death of 50% of animals within 30 minutes. LD_{100} is minimum dose that kills all animals.

This test also does not establish LD_0 or LD_{100}, which are also important measures of toxicity. Fig. 5-8 shows an example of the results of toxicity study. From it you can see what is meant by LD_0, LD_{50}, and LD_{100}.

Often it is useful to establish the whole–dose response curve. A general method is the graphic, log-probit method. A large group of animals is subdivided, and each subgroup is given a particular incremental dose. The percent of animals in each subgroup that manifest symptoms is determined. These percentages are transformed into probits* and plotted against the logarithm of the administered dose. The best straight-line fit of the data is determined graphically or mathematically. From this line the various LD (lethal dose) or TD (toxic dose) values are read along with their confidence limits. This method requires many more animals than the first method, and it also requires a fairly good estimate of the LD_{50} (or TD_{50}) in advance of the test. It also assumes that the dose-response curve will have the usual sigmoid shape. Its main advantages are that the whole–dose response curve can be defined and that endpoint measurements can be made at times distant from the time of injection.

*Miller, L. C., and Tainter, M. L.: Estimation of ED_{50} and its error by means of logarithmic probit graph paper, Proc. Soc. Exp. Biol. Med. **57:**261-264, 1944.

With a majority of radiopharmaceuticals it becomes impossible to devise meaningful toxicity studies. To get enough of the test substance to carry out the test may be impossible. To get the concentration high enough to have a reasonable injection volume may alter the radiopharmaceutical so drastically that the data would not be applicable. In these cases we rely on previously established toxicity studies for the various ingredients. Most of the ^{99m}Tc and ^{113m}In tracers are in this category. As an example, $^{113m}InCl_3$ is soluble only in acid solution. Thus, it is administered to patients in 0.05N HCl in small volumes. The injections must be done with care because infiltration of the dose will cause a local burning sensation. As the acid is diluted by the blood, it is neutralized, and the ^{113m}In becomes bound to circulating transferrin. In order for the tracer to work properly, it is necessary to use the acid vehicle. If we try to carry out a toxicity study with this radiopharmaceutical in a small laboratory animal, we will merely be observing the results of disturbing the animal's blood pH and blood volume. The data would not be informative about the toxicity of $InCl_3$. Acute toxicity tests that are used for regular pharmaceuticals are almost never directly applicable to radiopharmaceuticals.

The safety test is probably one of the most meaningful of the toxicity tests for use with
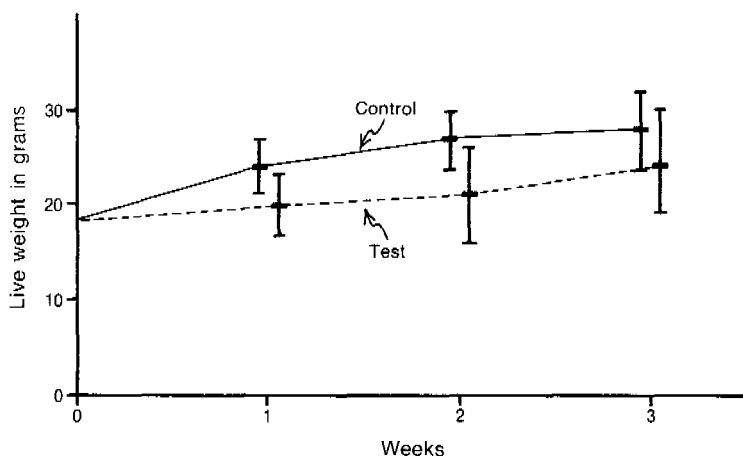
Fig. 5-9. Example of safety test data suggesting that drug probably has some inhibitory effect on growth of mice. Data are for stannous pyrophosphate given in weekly doses equal to 3,000 times the usual human dose.

radiopharmaceuticals. A group of six growing laboratory mice are weighed and injected intraperitoneally with a human dose of the radiopharmaceutical, while a control group are given the same volume of sterile saline for injection, U.S.P. This is repeated at weekly intervals for up to three injections. One week after the last injection, the animals are weighed (Fig. 5-9). The mean weights of the test animals are compared to those of the control animals. If some toxic ingredient is contained in the radiopharmaceutical, its presence will be suggested by difference in weights of the two groups. Even this test may not be applicable to radiopharmaceuticals. In the example of $^{113m}InCl_3$, the test animals would be affected by the acid in the vehicle; however, this test might be used if the acid were first neutralized before the injection. Even then, the results would have to be considered carefully because the toxicity of insoluble indium is significantly greater than the toxicity of indium that becomes bound to transferrin. This test is useful for checking for extraneous toxic ingredients that may have gotten into the preparation inadvertently.

Chronic toxicity tests, in general, have no place in the testing of radiopharmaceuticals. We know of no example in which a radiopharmaceutical is administered chronically to patients, as are other drugs.

Introducing new radiopharmaceuticals

Nuclear medicine is still a relatively new field of medical practice; thus, the applications of tracer techniques to the solution of medical problems have just begun. New tracer tests will be appearing frequently for many years. These new tests often require that a new radiopharmaceutical be provided to clinics that have not used the tracer previously. For limited local trials, it may be sufficient to obtain approval to start up the new test from a local committee who reviews the protocol, formulation, and animal studies to evaluate the risk-to-benefit ratios associated with the introduction of the new test. When it is expected that the test will have wider applicability and especially if the radiopharmaceutical or the reagent kits will be shipped out-of-state, then the promoter of the new radiopharmaceutical (or new formulation

Table 5-4. Practical considerations for the introduction of a new radiopharmaceutical

Consideration	Questions to be explored
Economics	Will the new radiopharmaceutical pay off?
Supply	Can the tracer be supplied when and where needed?
Quality control	Are quality control tests available, and are they practical for routine use if needed?
Education	Are the clinicians prepared to effectively use test results?
Instrumentation	Is appropriate detection equipment available?
Procedure	Has routine procedure been developed and evaluated?
Troubleshooting	What do you do when tracer does not perform properly? Can misperformance be detected?
Follow-up studies	Can follow-up studies be obtained to demonstrate effectiveness?

of an existing radiopharmaceutical) is obliged to file an application with the federal government. These are filed with the Bureau of Oncology and Radiopharmaceuticals of the Food and Drug Administration (FDA). The initial filing often is the Investigational New Drug Application (IND), and the subsequent filing is the New Drug Application (NDA).

In addition to legal considerations, many practical problems must be dealt with. These are summarized in Table 5-4. Once a decision has been made to introduce a new tracer, many questions are raised that need definitive answers so that the new tracer test can be wisely used. A list of several of these questions is presented on p. 87.

THE IND

Federal control of new radiopharmaceuticals is established with the use of a legal instrument called an Investigational New Drug Application. The document is a filing with the FDA of information showing how the tracer is prepared and how it is to be used. All aspects of formulation, labeling, quality control testing, animal studies, bibliography, and plans for clinical trials are detailed.

Critical questions to be answered
prior to widespread use of a radiopharmaceutical tracer

1. What is (are) the purpose(s) of this radiopharmaceutical?
2. What is the evidence that it is effective in fulfilling its intended purpose?
3. What is the normal distribution in experimental animals? In normal man?
4. What are the indications for use of the radiopharmaceutical?
5. What are the contraindications for its use?
6. How exactly is the radiopharmaceutical prepared?
7. What quality control tests are necessary and how exactly are they performed and evaluated?
8. How is the radiopharmaceutical to be used? What is the required dose in ml? μCi? μg?
9. What is the safety factor and the evidence that this safety factor is valid and applicable?
10. What are the side effects and untoward reactions and their probability of occurrence?
11. What ancillary drugs are required, if any? How, when, and in what dosage levels are they administered, and what are the problems associated with the use of these drugs?
12. Can this radiopharmaceutical be administered repeatedly? What are the results of repeated animal injections, if applicable?
13. What is the radiation dose? Whole body? Critical organs? Gonads?
14. What is the record of this radiopharmaceutical? Number of administrations? Percentage of beneficial results? Percentage of misleading results? Percentage of patient reactions? Descriptions of patient reactions?

After an IND becomes accepted by the FDA, it is the IND that controls the use of the radiopharmaceutical. That is, the holder of the IND is expected to carry out the formulations, quality controls, and clinical trials as outlined in the IND and report the results back to the FDA. If changes become necessary, the holder is obliged to request a modification of the IND. This procedure can work well for new radiopharmaceuticals, especially if the applicant presents an efficient and reasonable plan in the application.

On the other hand, the IND procedure is not working so well for established radiopharmaceuticals that need reformulation or those which are needed in clinical settings not covered in the original IND. The administrative logistics often restrict the use of needed tracer tests. The preparation of a new IND or amending an existing IND is often lengthy and expensive. Frequently, the income from the radiopharmaceutical does not justify the expense of preparing and filing the additional papers with the FDA. For example, the demand for adrenal studies in New Mexico is probably less than ten patients per year. This is hardly enough to justify filing an IND on an adrenal localizing agent, even though the details for preparing and testing the tracer are well explained in the literature. Thus, if no one obtains an NDA on such an agent, it is never marketed, and some patients will go without the advantages offered by the more specialized radioactive tracer tests.

Another problem with the IND process as it applies to radiopharmaceuticals is that it inhibits the solution of minor formulation problems. Frequently, problems are discovered with an existing formulation that can be simply rectified, but these are not instituted because the filing of the amendment necessitates too much of an investment of time and dollars. Often, such problems are avoided if the initial filing provides for some flexibility in the procedures.

CLINICAL TRIALS

The first clinical trials serve several purposes: (1) to test the hypothesis that the tracer will perform in man as expected from the animal studies, (2) to verify the proposed methodology, (3) to establish the biodistribution of the tracer in normal subjects as controls for

future studies in patients and to obtain data that can be used in refining the radiation dose calculations, and (4) to search for any possibilities of adverse reactions or toxicology. Since the use of radioactive tracers in normal subjects is irradiating the normal population, these studies are kept to an absolute minimum. If the first three subjects demonstrate reproducibility of the biodistribution, reveal no adverse effects, and verify the methodology, then this phase of the clinical trials may be halted. However, it may be necessary to carry out the tests in more normal subjects in order to determine normal ranges of critical values. An upper limit to this initial phase is probably around forty to a hundred subjects.

It is customary to examine the first subjects very carefully for any signs of toxicity. Blood pressure, heart and respiration rates, and temperature are monitored before and after each test. Also, blood and urine samples are checked for evidence of changes in renal or hepatic function.

The next phase of the clinical trials is usually directed toward patients known to have the disease that the test is designed to detect. These trials are especially aimed at testing the hypothesis that this pathology can be detected by the proposed procedure. These patients also provide data for further refinement of radiation dosimetry estimates. As with the normal subject, vital signs and blood and urine analysis are carefully checked for evidence of toxicity. Again, this phase of the clinical evaluation is limited to the number of patients required to provide statistically valid conclusions. Excessive testing only contributes to development costs that drive the eventual price of the tracer test upward.

The final phase involves more patients in several clinical settings. In contrast to the initial phases where the patients were selected based on whether they were normal or had the disease in question, these subjects are selected because there is a possibility of the disease. Each test is evaluated as to whether it was diagnostically useful and as to whether it produced any suspected symptoms in the subjects. Confirmation of the diagnosis is made subsequent to the tracer test. It is especially desirable to conduct this phase of the investigation so that the sensitivity and specificity of the test are measured.

This discussion of clinical trials is not necessarily consistent with FDA policy. Rather, it is based on our experience and reflects what we believe to be current scientific wisdom. Also, the suggested tests are outlined for new radiopharmaceuticals rather than for new INDs on existing radiopharmaceuticals or reformulation of existing radiopharmaceuticals. In these cases the minimum essential data should be obtained in the most cost-effective manner. The tests should demonstrate that the tracer works as predicted from previous experience.

A major purpose of an IND is to get data for the NDA filing. This should be done with the minimum number of cases required to establish safety and effectiveness. Massive amounts of data become difficult to control and costly to evaluate.

Replacing old radiopharmaceuticals

When it becomes scientifically obvious that a new isotope or a new tracer compound is superior to a currently used tracer, then an effort to switch should be made with dispatch. Current FDA policy does not encourage this. Also, mechanisms for removing radiopharmaceuticals from the NDA listing are not apparent. Compounds such as ^{203}Hg chlormerodrin remain on the list in spite of considerable evidence that better and safer tracers are available. To remove this compound from the listing would not create any diagnostic problems. On the other hand, ^{99m}Tc lung imaging agents have been long established as superior to ^{131}I MAA. The radioiodine compound should not yet be removed, however, because there are still times and places where a ^{99m}Tc product is not available, whereas the longer shelf-lived ^{131}I MAA can be obtained for emergency lung scans.

Adverse reactions
to radiopharmaceuticals

An adverse reaction is the unanticipated physiologic response of a patient to a radiopharmaceutical. Such a response is attributed to the vehicle rather than to the tracer because the chemical amount of the tracer is usually

inconsequential in comparison to the chemicals making up the vehicle. Adverse reactions may, at times, be **psychosomatic** in origin. Examples of adverse reactions are **anaphylaxis,** hives, bronchospasm, and other allergic manifestations: fever, headache, infection, stroke-like states, flushing of the skin, and metallic tastes in the mouth. In the case of **intrathecal** injections, the symptoms can include stiffness of the neck, headache, confusion, and aseptic meningitis. These symptoms have been traced in the past to contamination of the radiopharmaceuticals with pyrogens.

Adverse reactions are often associated with ancillary drugs used with the radiopharmaceutical. Lugol's solution, given to prevent radioiodine accumulation in the thyroid and administered in conjunction with compounds containing ^{131}I, can be responsible for adverse reactions in iodine-sensitive patients. Perchlorate and atropine, given to block $^{99m}TcO_4^-$ uptake in the choroid plexes and salivary glands and administered in conjunction with brain scanning procedures, may also contribute to adverse reactions.

Adverse reactions should be promptly and carefully investigated to prevent further incidence. The reports should be filed with *The United States Pharmacopeia,* who in turn report to the manufacturer, the FDA, and the Registry of Adverse Reactions maintained by the Society of Nuclear Medicine, Inc. The Registry is of great importance because it allows for the documentation and analysis of reactions that occur with very low frequency.

Overdosing and underdosing

To assure that patients get the appropriate dose of a radiopharmaceutical requires careful checking of the radioactivity prior to each administration. If the dose is injected prior to its calibration time, or if an adult dose is given to a child, overdosing occurs. In such cases, no effect of the excess radiation is expected; however, the images may be inferior if the count rates are outside the optimum range for the procedure that is used. Excessive overdosing is rare but has been documented. For example, a 200 mCi dose of ^{198}Au was administered instead of the indicated 200 μCi dose. The patient eventually died of radiation poisoning.

In the past, when ^{131}I MAA and ^{113m}In or $^{99m}Tc\text{-}Fe(OH)_3$ flocs were in more widespread use as lung scanning agents, overdoses or toxic doses were occasionally reported. These cases usually were seen when several milligrams of the tracer were administered to young or very sick patients already suffering from pulmonary hypertension. Apparently, the additional obstruction to pulmonary blood flow in these patients was not tolerated. The patients who died exhibited the same symptoms observed when mice were overdosed with these particles: faintness, cyanosis, tachypnea, agitation, and diaphoresis progressing to sinus tachycardia and death. With current agents, ^{99m}Tc microspheres and ^{99m}Tc MAA, which have higher specific activities and thus fewer particles per dose, no new cases of overdose of lung scanning particles have been reported.

Underdosing can result in insufficient data for a successful study and thus the patient is irradiated without benefit. Underdosing usually results from calibration error, infiltration of the dose, or adherence of the tracer to the syringe or needle. The counting of spent syringes prior to their disposal is a way of checking for hang-up of the tracer in the syringe. As was pointed out in Chapter 3, underdosing with lung scanning particles leads to patchy pictures because individual particles can be imaged.

Injection problems

Faulty injection techniques can adversely affect the results of tracer studies. Dynamic studies, for instance, often require precisely controlled injection procedures. Usually, this requires that the dose being injected be contained in a volume of no more than 1 ml and that a standardized procedure, such as the Oldendorf procedure, be used.* When particulate radiopharmaceuticals are injected, special precautions are required. Blood withdrawn into the syringe tends to clot more rapidly because of the catalytic action of the particles. Some-

*Various injection techniques are described by Robinson, R. G.: Standardization of the input function. In Rhodes, B. A., editor: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.

times radioactive emboli are produced and injected into the patient. These show up as obvious "hot spots" on the lung scan. To avoid this, syringes in which blood is allowed to stand for more than a minute are discarded, and a new dose is obtained for the study. Lung scanning agents should be administered slowly over several breath cycles while the patient is supine. This gives a distribution of the tracer more representative of the average perfusion to the lungs. The dependent portion of the lungs receives more blood flow, so consistent positioning during injection of a lung scanning agent is important.

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Radiation therapy with radiopharmaceuticals

Design

This is a discussion of radiation therapy using radiopharmaceuticals, not of the use of various nuclides as sealed sources or pieces of wire. The behavior of radiopharmaceuticals used for radiation therapy must be very well understood to avoid radiation dose to other than the intended areas.

When radiation therapy is the intended use of a radiopharmaceutical, the design criteria change slightly. We are still intending to use easily produced, available, inexpensive radionuclides of high specific activity. Most important is that the target-to-nontarget ratio be extremely high in order to minimize the danger to other organs. Most radiopharmaceuticals in use now do not have the high ratio needed to satisfy this criterion. Since we do not intend to minimize the radiation dose to the target but rather to maximize it, different radiation characteristics must be sought. The dose should be delivered fairly quickly, so the effective half-life should be short, primarily because of the physical half-life. The material should be a beta emitter with no external radiation, so that the dose can be localized in the patient and so that his attendants and visitors do not get an unwanted dose. If the material cannot be made to remain at the site of localization, it must be removed from the body quickly, as by hydrating the patient or by using cleansing enemas.

131I

By far the most radiation therapy in nuclear medicine is performed with ^{131}I. Iodine therapy is practiced on patients suffering from hyperthyroidism, who are not terminal patients being treated palliatively but are people who have long lives ahead of them. They must be treated carefully to avoid the possibilities of cancer induction and genetic damage. Under no circumstances should a pregnant woman be treated because iodine crosses the placental barrier and can accidentally treat the thyroid of the fetus, leaving it athyroid. Iodine therapy is also used to treat thyroid cancer, usually after surgery. It is useful for ablating remaining thyroid tissue and for treating metastatic thyroid tissue. The iodine is used in the iodide ion form, with no added carrier. The thyroid may be stimulated before the dose is administered to thyroid cancer patients. The iodine is a normal constituent of the thyroid and its hormones, so the mechanism for uptake for therapy is the same as that of other iodine incorporation into thyroid hormone. The many gamma rays of ^{131}I create a radiation hazard to the people surrounding the patient. ^{125}I has also been used in thyroid therapy.

^{32}P sodium phosphate

Phosphorus 32 is a pure beta emitter with a 14.3-day half-life. It has been used in the soluble sodium phosphate form for the treatment of several hematologic conditions such as leukemia and polycythemia vera. It is administered either orally or intravenously and concentrates in the blood cell precursors of the marrow where there is rapid proliferation of cells. There is some evidence that the treatment can cause leukemia in people who do not have it and that chemotherapeutic and other treatments may be preferred (Table 6-1).

Colloids

Phosphorus 32 in the insoluble colloidal form of chromic phosphate and gold 198 as the colloid have been used to treat effusions, both of

Table 6-1. Therapeutic uses of radionuclides

Nuclide	Chemical form	Target organ	Indications
^{131}I	I^-	Thyroid	Thyrotoxicosis, thyroid cancer, thyroid cancer metastasis
^{32}P	Sodium phosphate	Bone marrow	Leukemia, polycythemia vera
^{32}P	Chromic phosphate	Body cavities	Malignant effusion
^{198}Au	Colloidal gold	Body cavities	Malignant effusion

the synovial membrane in rheumatoid arthritis and of the peritoneal cavity often after incomplete surgery. The colloid, diluted in saline to fill the space, is instilled into the cavity in question. The dose is delivered on the surface of the cavity to which the colloid adheres. In peritoneal instillation it may be that ^{198}Au confers less harmful doses to other structures in the patient; because of its shorter half-life, it spends more of its lifetime in the correct cavity and less as a colloid that has passed through the diaphragmatic surface and made its way into the liver. ^{32}P, on the other hand, is a pure beta emitter, whereas the gold emits a gamma ray at 410 kev, which presents a hazard to the surrounding tissues. All the colloids behave similarly, though not identically because of particle size differences. It is possible to image the cavity into which the ^{32}P colloid is to be instilled by giving a tracer dose of ^{99m}Tc sulfur colloid prior to the ^{32}P procedure.

Handling therapy patients
ASSURANCE OF RADIOISOTOPE DOSAGE

Some physicians will prescribe the exact mCi dose and chemical form of the radionuclide to be used for therapy. At other times, it may be necessary for the technologist or radiopharmacist to assist with the calculation required for arriving at the required mCi dose. For example, in treating the thyroid with radioiodine, data from a previous radioiodine uptake study and estimation of gland size either from a radioisotope scan or palpation can be used to estimate the required number of mCi of ^{131}I to be administered to provide a given radiation exposure dose. A previous study of ^{99m}Tc sulfur colloid can sometimes be used to help estimate the required number of mCi of colloidal ^{32}P or ^{198}Au.

Once the radiation exposure dose is set and the mCi dose required to produce this exposure dose is estimated, the dose must be measured out and dispensed to the patient. Some clinics have policies that require two individuals to check each other to assure that both the calculations and the radioisotope measurements are correct. Great care is always taken to assure (1) that the correct mCi amount is measured out and administered, (2) that the dose is given to the correct patient, and (3) that appropriate radiation safety considerations are met. Radiation therapy, though usually less traumatic to a patient than surgery, is a procedure with consequences similar to surgery. To make a mistake with a therapy dose is a very serious matter similar in magnitude to operating on the wrong patient. Thus, it is often wise to request verification of calculations and measurements from a radiation physicist or nuclear medical scientist.

RADIATION SAFETY CONSIDERATIONS

The possibility of personnel radiation exposure during the drawing, handling, and measurement of therapy dose should be carefully considered. The same precautions required for handling diagnostic dosages are used. However, often a second trained person is available to survey the operation and monitor the radiation exposure levels with a hand-held survey meter.

With doses of ^{131}I larger than 30 mCi, hospitalization of the patient is required. The patient is placed in isolation until the body burden is less than 30 mCi. During this period, special procedures are followed to minimize radiation exposure to nurses and other health care personnel. Also, special procedures for disposal of radioactive body wastes and clothing are fol-

Fig. 6-1. Radioiodine solutions are being given to patient in lead-shielded cup and disposable straw (or pipette if straw is not available). Radiopharmacist discusses procedure with patient so that patient cooperation is assured.

lowed so that radiation contamination of the hospital environment is avoided.

TALKING WITH THE PATIENT

Each person who deals with a patient undergoing radiation therapy with a radionuclide has the responsibility to help make the procedure safe and effective by relating kindly and carefully to the patient. Patient cooperation is often best achieved by clear and precise communication with the patient. We have found that if we explain exactly what we are doing and why, the patients usually feel more at ease with the process.

When administering oral radioiodine solutions, often the solution is dispensed in a cup within a lead shield (Fig. 6-1). Absorbent papers are used to guard against spillage. If the reasons for use of this are explained, the patient usually will not be upset by what appears to be a strange procedure.

Fig. 6-2. Radioiodine container is rinsed with water two to three times. Patient is asked to drink washing to assure that total dose is taken.

After explaining the procedure to the patient, question him as to whether he has a settled stomach. If a patient is nauseated, it is wise to postpone oral doses of radionuclides. Also, instructions are given to assure that the patient takes all of the dose. The cup may be rinsed two to three times with water to assure that the whole dose is swallowed (Fig. 6-2). Avoid rinsing the cup with saline solution or warm water because this can induce nausea. Once the dose is administered, it is expedient to release the patient so that exposure to self and other individuals in the nuclear medicine clinic is minimized. Radioactive patients interfere with counting instrumentation by increasing and causing unpredictable fluctuations in background radiation levels.

Suggested readings

Brucer, M.: From surgery without a knife to the atomic cocktail. Vignettes in Nuclear medicine, No. 2, St. Louis, 1966, Mallinckrodt Chemical Works.

Larose, J. H.: Radionuclide therapy. In Early, P. J., Razzak, M. A., and Sodee, D. B., editors: Textbook of nuclear medicine technology, St. Louis, 1975, The C. V. Mosby Co.

Silver, S.: Radioactive nuclide in medicine and biology, Philadelphia, 1968, Lea & Febiger.

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Radiation dosimetry

EARLY OBSERVATIONS OF RADIATION EFFECTS

The discovery of ionizing radiation was soon followed by the discovery of its acute harmful effects. The story is told that Marie Curie's professor proudly displayed the first sample of the new element, radium, in a small vial attached to his lapel. A short time later, the first radiation burn was observed. To verify the association between radioactive elements and localized erythema, experimenters taped pieces of the new metal to their skin to observe the result. Their experiments proved that exposure to radiation can indeed cause burns to the skin. Can you imagine the response of a current radiation safety committee to such an experiment?

The association between radiation exposure and cancer took longer to discover. A major epidemiologic study of radium–watch dial painters revealed that the dial painters who tipped their brushes to a fine point in their mouths must have swallowed large amounts of radium. Some of the ingested radium was sequestered in bone, where it remained for years. The incidence of bone cancer in this group was significantly greater than expected for the general population. An increased incidence of thyroid cancer has likewise been observed in adults who underwent neck irradiations during childhood.

REVIEW OF RADIATION BIOLOGY

The toxic effects of most drugs are demonstrated only when a threshold level of the drug is exceeded. An examination of a typical sigmoid dose-response curve such as the one studied in Chapter 5 reveals this threshold amount as the LD_0 or TD_0. When investigators tried to define such a curve for long-term radiation effects, no threshold could be determined. Thus, it is generally assumed that the probability of radiation carcinogenesis and radiation-induced genetic abnormalities is never zero, regardless of how low the exposure dose. We know that the rates become too low to measure by most feasible techniques. We know that the time between exposure and manifestation of symptoms increases as the dose decreases. We know that at low exposure rates biologic repair mechanisms operate to correct some of the damage. Thus, we proceed knowing that there is some risk associated with all radiation exposure. This is accepted just as we accept the risks of riding in a car or walking across the street.

Because we realize that the use of radiation always involves some risk, one of our guiding principles behind the compounding and administration of radiopharmaceuticals is that every attempt must be made to keep the radiation exposure to workers and patients at a level as low as possible, consistent with the production of a satisfactory examination. The maximum cumulated whole-body dose for radiation workers as a function of age, N, is $5(N - 18)$ **rem,** or 5 rem per year. The general public should not be exposed to more than 0.1 of this amount except for medical purposes. To assure that we are careful, exposure doses are monitored, and lifetime records of accumulated exposures are maintained. Almost no other industry has the safety records of the nuclear industry because of the strict adherence to this policy for safeguarding both the public and radiation workers.

Ionizing radiation is defined as radiation that

can cause **ionization** in the absorbing medium. Charged particles, photons, and other products of natural and induced nuclear reactions are ionizing radiation. In the course of their slowing and stopping in any medium, they leave a track of ionized atoms behind. The electrons are removed from atomic shells in the path of the particle. This ionization may lead to disruption of the molecule containing that atom or to the molecule transferring its charged status to another molecule, damaging it. Most biologic systems contain high percentages of water, so the water is what is most likely to be ionized by the impinging radiation. The water then transfers its excited ionization to another molecule that it is surrounding, leading to the radiation damage of the second molecule. At low radiation dose rates, molecules can possibly repair themselves; at high dose rates, they are irreparably damaged (at these dose rates complicated biologic molecules will be damaged beyond any functional capability). At intermediate dose rates the molecules may be damaged and unable to be repaired, so that they malfunction and cause problems, sometimes immediately or sometimes much later.

The effects that have been accorded to ionizing radiation are acute burns, dermatitis and hair loss through chronic effects such as premature aging, and carcinogenesis. Genetic effects are also possible, in which succeeding generations are affected, while the actual absorber of the radiation is apparently unaffected.

REVIEW OF THE PROPERTIES OF RADIOACTIVE MATERIALS AND ABSORPTION OF RADIATION

In preparation for learning about how radiation doses can be calculated, it is necessary to review the properties of the particles emitted during radioactive decay and how they are absorbed (Table 7-1). The first of these is the alpha particle, which is a helium nucleus, ^4He. It is massive, has a range of a few layers of skin, and is not used in nuclear medicine. Alpha-particle emitters are dangerous when they are incorporated in tissue or bone because then the energy is absorbed in that tissue or bone. Alpha emitters have been indicted for radiation damage to the radium–watch dial

painters and, medically, to patients in whom thorium dioxide (Thorotrast) was used as a liver contrast agent.

Beta particles are electrons emitted from the nucleus either as positrons or negatrons. They have a range of a few millimeters of tissue in which they deposit their energy, so they are not useful radiations for nuclear medicine; however, they are often present as part of the radiation coming from the nuclides in use. The positron is not ordinarily absorbed but instead meets an electron at the end of its path; the two annihilate, causing two 511 kev photons, which are absorbed according to the rules for photons. An energetic electron leaves a trail of ionization in its wake as it slows down. All electronic or beta radiation from a decaying atom behaves the same way and can be treated as depositing its energy within a few millimeters of its creation.

Gamma radiation consists of photons. These particles are pure energy with no mass and have appreciable ranges in tissue so that they can be detected noninvasively. All photons of these energies, whether gamma rays from nuclear decay or x rays created from the de-excitation of atomic electrons, behave similarly. In the energy ranges that are generally used in nuclear medicine, photoelectric absorption and Compton scattering are the mechanisms for transferring energy from the photon to the surroundings. Both of these cause ionization of the surroundings, over a distance as appreciable as many centimeters in tissue. At the lower energy ranges, below 10 kev, the range is short, so the dose from low-energy photons is mathematically treated like the dose from beta particles.

When a nucleus decays, it is adjusting itself from a higher energy state to a lower and more stable state. Its decay usually affects the nucleus, often changing its chemical identity and the electronic shells surrounding it.

In order to discuss radiation dose it is necessary to take into account all the emanations from the nucleus and its electronic shells and to know what the proportion of each is. These facts have been well documented, since they are part of the "signature" of a particular radioactive state, and they are printed in tabular

Table 7-1. Dosimetry calculations for technetium 99m sulfur colloid*

Radiation	Energy (mev)	$\Delta_{np}\phi_{np}$ (gram·rad/μCi·hr)	Δ_p	$\phi_{(L \leftarrow L)}$	$\Delta\phi_{(L \leftarrow L)}$	$\phi_{(L \leftarrow S)}$	$\Delta\phi_{(L \leftarrow S)}$
Internal conversion electrons							
M, γ_1	0.0017	0.0036					
K, γ_2	0.1195	0.0225					
L, γ_2	0.1377	0.0032					
M, γ_2	0.1401	0.0011					
K, γ_3	0.1217	0.0025					
L, γ_3	0.1399	0.0009					
M, γ_3	0.1423	0.0003					
L x rays	0.0081	0.0000					
Auger electrons							
KLL	0.0155	0.0005					
KLX	0.0178	0.0002					
KXY	0.0202	0.0000					
LMM	0.0019	0.0004					
MXY	0.0004	0.0010					
X rays ($>$0.01 mev)							
Kα1	0.0184		0.0017	0.82	0.0014	0.0000	0.0000
Kα2	0.0183		0.0008	0.82	0.0007	0.0000	0.0000
Kβ1	0.0206		0.0005	0.78	0.0004	0.0000	0.0000
Kβ2	0.0210		0.0001	0.77	0.0001	0.0000	0.0000
Gammas							
γ_1	0.0021		0.0000	1.00	0.0000	0.0000	0.0000
γ_2	0.1405		0.2643	0.16	0.0423	0.0071	0.0019
γ_3	0.1427		0.0001	0.16	0.0000	0.0071	0.0000
		$\Sigma\Delta_{np}\phi_{np} = 0.0362$			$\Sigma\Delta\phi_{(L \leftarrow L)} = 0.0449$		$\Sigma\Delta\phi_{(L \leftarrow S)} = 0.0019$

*Calculations are based on output data, biodistribution data, and phantom geometry; courtesy Roger J. Cloutier.

form in several sources, the most accessible of which is the MIRD tables. For each nuclide listed, there are two tables and a schematic drawing. An example is shown in Fig. 7-1. The drawing shows the parent nucleus, the various energy levels, and the radiations connecting them, as well as the identity of the daughter or product nucleus. The first of the tables, labeled "Input Data," describes the kinds of radiation (beta and gamma) that are emitted by the nucleus, their relative frequency per disintegration as a percentage, their energy in mev, and some comments, such as the percentage of internal conversion and which electrons are involved. The second table, labeled "Output Data," is a list of *all* the radiation emitted

from the whole atom. This list is longer than the list in the first table because it contains, in addition to the previously listed nuclear radiations, all the conversion electrons, x rays, and Auger electrons. Again, there is a column for the mean number per disintegration, N_i, expressed as a fraction, the mean energy (E_i), which is the same as the energy for the gamma rays but which differs from the maximum energy for the beta particles (there is no interest in neutrinos for radiation dosimetry), and a quantity called $\Delta_i = 2.133 \, n_i\overline{E}_i$, where the constant 2.133 incorporates the conversion factor of 1 μCi·hr = 1.332 × 10^8 disintegrations and the conversion factor of 100 ergs = 6.25 × 10^7 mev to give units for Δ_i of gram·rads/μCi·hr,

Chromium 51

Electron capture
decay
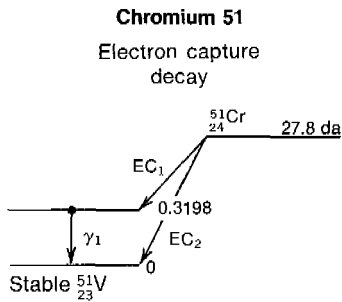
INPUT DATA			
Radiation	%/dis-integration	Transition energy (mev)	Other nuclear parameters
Electron capture-1	9.	0.432	Allowed
Electron capture-2	91.	0.752	Allowed
Gamma-1	9.	0.3198	M1 + 3% E2, $\alpha_k = 0.0015$

OUTPUT DATA			
Radiation (i)	Mean number/disintegration (n_i)	Mean energy (mev) $(\bar{E}_i)$	$\Delta_i \left(\dfrac{\text{gram} \cdot \text{rad}}{\mu\text{Ci} \cdot \text{hr}}\right)$
Electron capture-1	—	—	·
Electron capture-2	—	—	·
Gamma-1	0.0899	0.3198	0.0612
K int. con, electron, gamma 1	0.0001	0.3143	0.0001
K α-1 x ray	0.129	0.0050	0.0014
K α-2 x ray	0.0659	0.0049	0.0007
K β-1 x ray	0.0225	0.0054	0.0003
K β-2 x ray	0.0003	0.0055	0.0000
KLL Auger electron	0.561	0.0044	0.0053
KLX Auger electron	0.124	0.0049	0.0013
LMM Auger electron	1.53	0.0005	0.0016
MXY Auger electron	3.22	<0.0001	0.0000

Fig. 7-1. Decay scheme for ^{51}Cr with MIRD data tables. (From Dillman, L. T.: J. Nucl. Med. **10**[suppl. 2]:1-32, 1969.)

where the rad equals 100 ergs deposited in 1 gram of tissue.

Dosimetry calculations
PHYSICAL AND BIOLOGIC CONTRIBUTIONS

The aim of this section is not to make dosimetry theorists or even experts of the readers, but to make it possible for them to consider the various important parts of a dose calculation and to perform such a calculation. Because the MIRD scheme proposed by The Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine, Inc., is now so nicely documented, with new simplifications coming out periodically and with calculations on new radiopharmaceuticals being performed, reviewed, and published, this chapter will examine dose calculations from the MIRD viewpoint. The notation and vocabulary used in the MIRD publications will be used here. The methods and discussion can be generalized to radiopharmaceuticals as yet unheard of.

The dose equation will be stated, its parts examined carefully and separately, and then the parts returned to the whole in a sample calculation.

The terms you have heard associated with radiation dosimetry are the roentgen, the rad, and the rem (roentgen equivalent man). The **roentgen** (r) is a unit of emitted dose, defined

to be the quantity of x or gamma radiation such that 1 esu of ions is created in 1 ml of air at standard temperature and pressure (0° C and 760 mm pressure), which is 0.001293 gram of air. The rad expresses absorbed dose of any kind of radiation and is equal to the absorption of 100 ergs of radiation energy per gram of matter. The rem gives the equivalent of any type of radiation to that which would deliver 1 rad from x or gamma radiation. For tissue, all three units are essentially equal. One should, however, be careful to use rads in discussion of absorbed dose.

To calculate the dose to an organ, it is necessary to consider the sources of radiation to that organ. Beta radiation and low-energy gamma radiation are essentially nonpenetrating radiations with a short range, so any dose conferred on an organ from these radiations must come from sources within the organ. If the concentration of the radioactive material in the organ is essentially zero, then there is no dose to the organ from nonpenetrating radiation. Gamma radiation, on the other hand, acts at a distance, so the distances from the **target organ** to the source organ must be considered, as well as the geometry of each. In the MIRD scheme, a hypothetical construct known as reference man (Fig. 7-2), who is actually bisexual, has been used to make the geometric factors required to
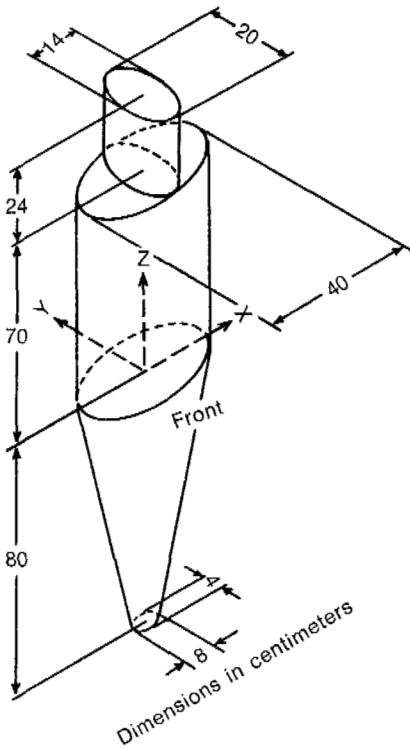
Fig. 7-2. MIRD reference man (see text).

consider the effects of a source, for example, in the liver and its effect on organs such as the spleen, thyroid, and brain. Thus, it is seen that every dose calculation will contain contributions from nonpenetrating and penetrating radiation, and contained in the latter is a geometric factor.

The general equation can be given by

$$\overline{D_T} = \frac{\tilde{A}_T}{m_T} \sum \Delta_{np}\phi_{np} + \sum_s \frac{\tilde{A}_s}{m_T} \sum \Delta\phi_{(T \leftarrow S)} \quad (1)$$

where
- T stands for target
- S stands for source
- $\overline{D_T}$ = total radiation dose to target (rads)
- $\tilde{A}_T$ = cumulated activity in target (μCi · hr)
- m_T = mass of target in grams
- $\tilde{A}_S$ = cumulated activity in source (μCi · hr)
- $\Delta_{np}\phi_{np}$ = absorbed fraction for nonpenetrating radiation
- $\Delta\phi_{(T \leftarrow S)}$ = absorbed fraction in target as a result of radiation emanating

from source. The target's own radioactivity must be considered in this sum, so there will be a term $\Delta\phi_{(T \leftarrow T)}$ if the target itself is radioactive

Δ = intensity of transition
ϕ = absorbed fraction

The physical data for the particular nuclide gives all the information for the Δ's. These are tabulated in the output data table. For nonpenetrating radiation, $\phi_{np} = 1$. The MIRD tables in Pamphlet No. 5 contain the data calculated from reference man's geometry *and* the energies of the gamma rays involved that are put together to give $\phi_{(T \leftarrow S)}$, where S is the source and T is the target. The pages of the pamphlet give the source organs. The target organs are listed down the side, energies vary across the page. Some laboratories have adapted all of this for the computer, but if you do not have access to such a system, you must interpolate linearly in order to get ϕ's for energies not listed. MIRD Pamphlet No. 11 has gone further to combine all the $\frac{\Delta\phi}{m_T}$ (T ← S) terms for a particular nuclide for all the source and target organs into a term called S, the absorbed dose per unit cumulated activity. S incorporates, then, all the data from the nuclide as to its radiations and from the reference man data for the organs in question. In terms of S:

$$\overrightarrow{D_T} = \sum A_S S_{(T \leftarrow S)} \quad (2)$$

In the following example, the S factor will be calculated and also drawn from the table in Pamphlet No. 11.

Notice that so far nothing has been said about the distribution of the radiopharmaceutical in the patient or about the half-time of residence in the patient. These are the factors that are combined in the term labeled Ã, the cumulated activity. These are the factors to which much of the ongoing dosimetry research has been directed.

The cumulated activity in μCi · hours is a number representing just that: the number of μCi in residence for how many hours. One can, for example, plot a curve of activity versus time for an organ as shown in Fig. 7-3. The cumulated activity would be the area under the
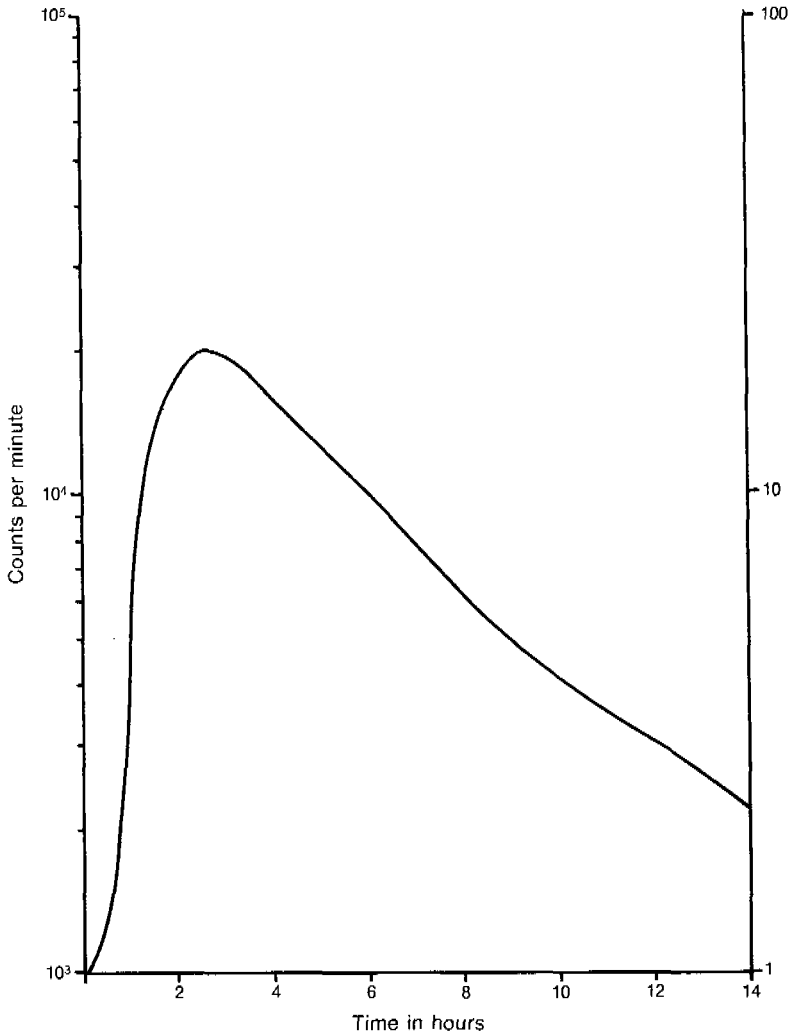
Fig. 7-3. Idealized activity-time curve for radioactive tracer in given organ of body.

curve. Very often the material is taken up quickly, as after a bolus injection, and then is removed slowly, following one or more exponential decay curves, as in the example pictured in Fig. 7-4. The contribution of each of the exponential segments can be determined as to its half-time and percentage of the total at $t = 0$. In this case as well, the cumulated activity is the area under an activity-versus-time curve.

If one is dealing with human data, it is usually not possible to get samples of the patient to find out the percentages of the dose contained in the various organs. Therefore, external counting, using standards for comparison, is often used. The standards usually cannot be simple because the organs themselves are not, so elaborate phantoms may be constructed for comparison (Fig. 7-5). Blood, urine, and fecal samples may also be obtained to help quantitate the amount remaining in the body at a particular time. It is usually helpful as well to have in mind a mathematical model of the kinetics of the radiopharmaceutical in the
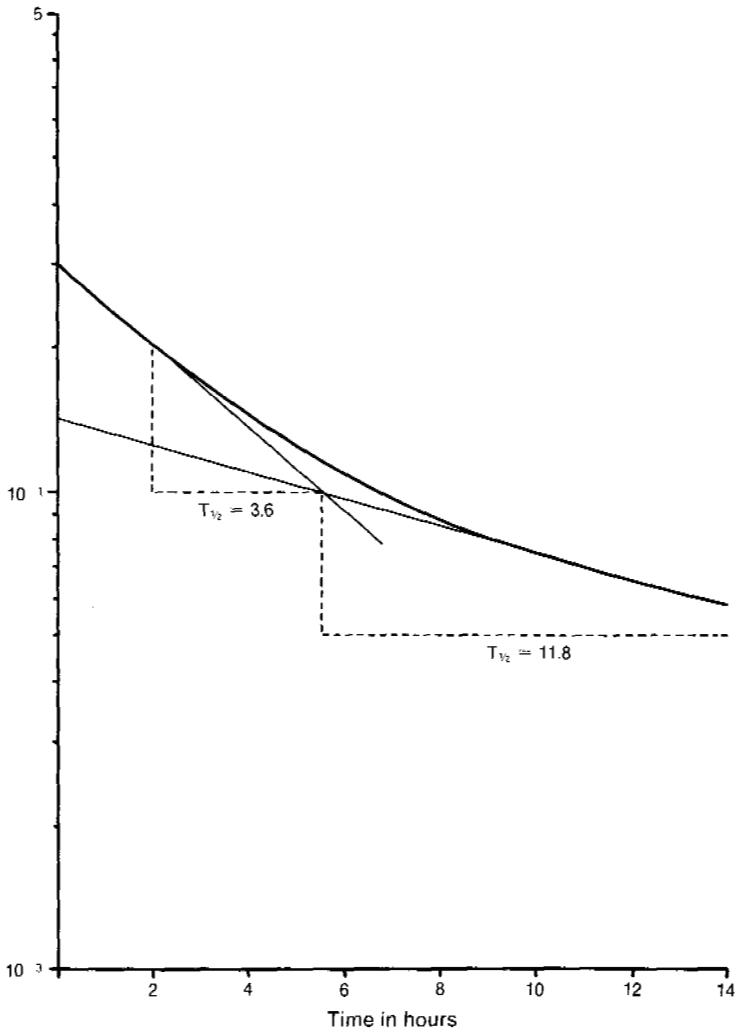
Fig. 7-4. Biexponential decay or clearance curve for radioactivity in organ.

organ. Animal studies can be very helpful in the formulation of such models. It must be remembered that although the data from the system seem to fit a theoretical model, this model is not necessarily a true model for the organ.

The cumulated activity has a contribution from the behavior of that element in that chemical form in the body and a contribution from the physical half-life of the particular isotope of the element that has been chosen. This can be used in many ways to work from the behavior of one isotope to another. It is not neces-

sary to start all over again to determine cumulated activity for ^{123}I once the data for ^{131}I are known. It is sufficient to account for the different physical half-lives. Of course, scrupulous care must be taken to be sure the chemical forms are identical.

All elements of a dose calculation can now be assembled. The physical data for the nuclide involved are incorporated in the Δ term, along with data from reference man in the ϕ term, particularly, and in the m_T term. Data about the behavior of this chemical form is used in $\tilde{A}$, in $\tilde{A}_T$ for the target for nonpenetrating radia-

Rods

Well

Fig. 7-5. Thyroid phantom, available from Picker Corp.
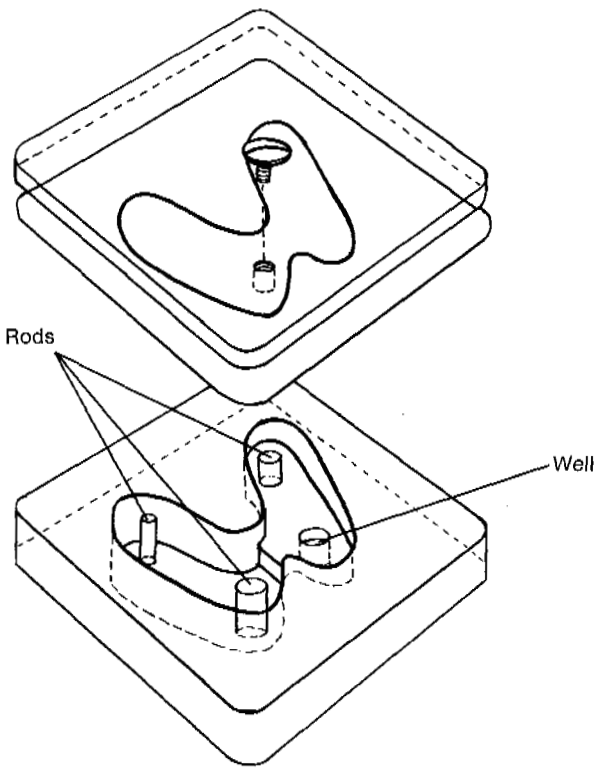
tion, and in $\tilde{A}_S$ for the sources for penetrating radiation, along with physical half-life data.

SAMPLE CALCULATION

For the sample calculation, ^{99m}Tc sulfur colloid as a liver scanning agent has been chosen. A certain simplicity occurs because the agent can be presumed to go to the liver, spleen, and bone marrow and to remain there for as long as predicted from physical decay calculations. The input data, output data, and decay scheme are given in Fig. 7-6. Our problem is to calculate the dose to the liver from the intravenous injection of 3 mCi of ^{99m}Tc sulfur colloid. The important terms in the equation are those accounting for nonpenetrating dose to the liver from the liver, penetrating dose to the liver from the liver, and penetrating dose to the liver from the spleen. The bone marrow contributes an insignificant amount.

$$\overline{D}_L = \frac{\tilde{A}_L}{m_L} \sum \Delta_{np}\phi_{np} + \frac{\tilde{A}_L}{m_L} \sum \Delta\phi_{(L \leftarrow L)} + \quad (3)$$

$$\frac{\tilde{A}_S}{m_L} \sum \Delta\phi_{(L \leftarrow S)}$$

Let us consider $\tilde{A}_L$ and $\tilde{A}_S$ first. The question

INPUT DATA

Radiation	% /disinte-gration	Transition energy (mev)	Other nuclear parameters
Gamma-1	98.6	0.0022	E3, α very large
Gamma-2	98.6	0.1405	M1, α₀ ~ 0.10, K/L = 8.1
Gamma-3	1.4	0.1427	M4, α₀ ~ 29 (T), α ~ 9.19 (T)

OUTPUT DATA

Radiation (i)	Mean number/ disinte-gration (n_i)	Mean energy (mev) (Ē_i)	λ_i (gram·rad / μCi·hr)
Gamma-1	0.00	0.0021	0.0000
M int. con. electron, gamma-1	0.986	0.0017	0.0036
Gamma-2	0.883	0.1405	0.2643
K int. con. electron, gamma-2	0.0883	0.1195	0.0225
L int. con. electron, gamma-2	0.0109	0.1377	0.0032
M int. con. electron, gamma-2	0.0036	0.1401	0.0011
Gamma-3	0.0003	0.1427	0.0001
K int. con. electron, gamma-3	0.0096	0.1217	0.0025
L int. con. electron, gamma-3	0.0030	0.1399	0.0009
M int. con. electron, gamma-3	0.0010	0.1423	0.0003
K α-1 x rays	0.0431	0.0184	0.0017
K α-2 x rays	0.0216	0.0183	0.0008
K β-1 x rays	0.0103	0.0206	0.0005
K β-2 x rays	0.0018	0.0210	0.0001
L x rays	0.0081	0.0024	0.0000
KLL Auger electron	0.0149	0.0155	0.0005
KLX Auger electron	0.0055	0.0178	0.0002
KXY Auger electron	0.0007	0.0202	0.0000
LMM Auger electron	0.106	0.0019	0.0004
MXY Auger electron	1.23	0.0004	0.0010

Technetium 99m

Isomeric level decay
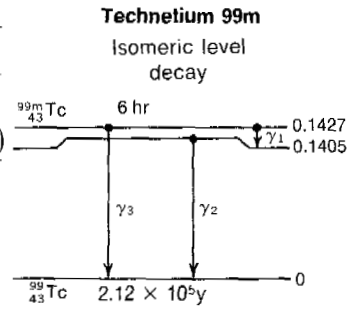
Fig. 7-6. Decay scheme for ^{99m}Tc with MIRD tables. (From Dillman, L. T.; J. Nucl. Med. **10**[suppl. 2]:1-32, 1969.)

we are answering is how much radiation for how long.

Physical half-life = 6 hours
Assumed biologic half-life = ∞
Distribution (assumed)
    Liver   90%
    Spleen   5%
    Bone marrow 5%
Activity, $A = 3$ mCi $= 3,000$ μCi
Effective half-time, $T_e =$ physical half-time = 6 hours
Cumulated activity in liver
    $\tilde{A}_L = 1.44 \times T_e \times A \times$ liver fraction
        $= 1.44 \times 6 \times 3,000 \times 0.90 = 23,328$
        μCi $\cdot$ hr
Cumulated activity in spleen
    $\tilde{A}_S = 1.44 \times T_e \times A \times$ spleen fraction
        $= 1.44 \times 6 \times 3,000 \times 0.05 = 1,296$
        μCi $\cdot$ hr
$m_L =$ mass of liver in reference man = 1,800 grams

Then a table must be constructed to calculate $\sum \Delta_{np}\phi_{np}$ and $\sum \Delta\phi_{(L \leftarrow L)}$ and $\sum \Delta\phi_{(L \leftarrow S)}$. This is given in Table 7-1, and the sums made below. All of the quantities are fit into the dose equation:

$$\overline{D_L} = \qquad\qquad\qquad\qquad\qquad\qquad (4)$$

$$\left(\frac{23.3 \times 10^3 \; \mu\text{Ci} \cdot \text{hr}}{1.8 \times 10^3 \; \text{grams}} \right) \left(3.62 \times 10^{-2} \; \frac{\text{gram} \cdot \text{rad}}{\mu\text{Ci} \cdot \text{hr}} \right)$$

$$+ \left(\frac{23.3 \times 10^3 \; \mu\text{Ci} \cdot \text{hr}}{1.8 \times 10^3 \; \text{grams}} \right) \left(4.49 \times 10^{-2} \; \frac{\text{gram} \cdot \text{rad}}{\mu\text{Ci} \cdot \text{hr}} \right)$$

$$+ \left(\frac{1.296 \times 10^3 \; \mu\text{Ci} \cdot \text{hr}}{1.8 \times 10^3 \; \text{grams}} \right) \left(0.19 \times 10^{-2} \; \frac{\text{gram} \cdot \text{rad}}{\mu\text{Ci} \cdot \text{hr}} \right)$$

$= 0.468 + 0.581 + 0.00137$
$\overline{D_L} = 1.05$ rads for the dose to the liver from 3 mCi of ^{99m}Tc sulfur colloid, according to the assumptions of this calculation

To do the same calculation using the tables of Pamphlet No. 11, the addition numbers are:

$$S_{L \leftarrow L} = 4.5 \times 10^{-5} \text{ rads}/\mu\text{Ci} \cdot \text{hr}$$
$$S_{L \leftarrow S} = 1.056 \times 10^{-6} \text{ rads}/\mu\text{Ci} \cdot \text{hr}$$

The calculation is:

$$\overline{D_L} = \tilde{A}_L S_{L \leftarrow L} + \tilde{A}_S S_{L \leftarrow S}$$
$$= 2.33 \times 10^4 \times 4.5 \times 10^{-5} + 1.296 \times 10^{+3}$$
$$\times 1.056 \times 10^{-6}$$
$$= 1.048 + 0.00137$$
$$\overline{D_L} = 1.05 \text{ rads}$$

Summary

Dose calculations are usually made for whole body, the one or several organs that appear to get the highest percentage of activity, the gonads, and the bone marrow. In Table 7-2 it can be seen that the radiation doses received during some common nuclear medicine examinations are on the same order as those received from common x rays. Nuclear medicine perhaps confers the advantage that when static images are required, more views can be obtained without further radiation dosage.

It should be remarked that this discussion has been quite theoretical, even while pretending to be practical because there has been no consideration of the individual patient, the effect that factors such as diseases and drugs might have

Table 7-2. Absorbed doses in mrads

Procedure and views	Total body	Target organ	Bone marrow	Gonads Male	Gonads Female
Living 1 yr at sea level	100 mrem/yr				
Living 1 yr in Denver, Colo.	180 mrem/yr				
Brain scan, ^{99m}TcO$_4^-$, 15 mCi		550 (stomach)	450	350	400
Bone scan, ^{99m}Tc polyphosphate, 10 mCi		3,050 (bladder) (no emptying)	300	375	400
Skull films (AP, lateral)		1,400 (skin)	50	10	10
Skeletal survey (skull, cervical-dorsal-lumbar spine, pelvis, hips, femur, lower leg, elbow, arm)		2,000 (skin)	700	3,300	1,200

on the Ā term, or the variations from reference man. If a dose calculation on a particular patient is required, some attempt must be made to gather the requisite data in order to approximate the calculations. The calculations are made not as calculations on individual patients, but as a guide in the use of radiopharmaceuticals so that the risks associated with a given injection for a particular examination can be estimated. With these dose estimates, one isotope can be compared to another and one tracer to another on the basis of their radiation dose characteristics. The overall aim is to maximize the ratio of use-ful information per rad of exposure dose. One index of the ratio is the number of detectable photons per rad. If two alternative procedures are equal in other respects, the one giving the highest ratio is chosen.

Suggested readings

Kereiakes, J. G., and Corey, K. R., editors: Biophysical aspects of the medical use of technetium-99m, AAPM Monograph No. 1, Cincinnati, Ohio, 1976, American Association of Physicists in Medicine, Committee on Nuclear Medicine.

MIRD reports, New York, Society of Nuclear Medicine, Inc.

Production of radionuclides

The radioactive materials in use in nuclear medicine are almost all man-made.* They must be produced from materials we have at hand or can create. It was not possible to have other than naturally occurring radionuclides until the discovery of nuclear reactions and the clarification of the structure of the atom and the constituent parts of the nucleus. Some research had been begun in the 1930s, but the real spurt in growth came after World War II, when the data collected by the Manhattan Project were released, and the reactor began to be used for isotope production. Currently many radionuclides are also produced in cyclotrons and linear accelerators.

Activation of stable elements
CALCULATION OF PRODUCTION RATES AND REACTOR PRODUCTION

Many of the nuclides in use today are reactor produced (Fig. 8-1). The nuclear **reactor** can be viewed as a source of thermal or low-energy neutrons. Neutrons are neutral particles with a mass of 1 amu. Because they are without charge, they cannot be aimed into beams like charged particles. Instead, they are allowed to escape from the reactor elements and irradiate materials presented to them through ports that run down into the reactor core alongside the moderator tubes. The flux (amount of neutrons available for reactions) is highest at the core of the reactor.

When thermal neutrons impinge on many materials, they are absorbed into the nuclei, very often creating an unstable radioactive nucleus of the same chemical identity as the

*An exception is ^{40}K.

irradiated material. The induced radioactivity may also be used as a signature of the material irradiated and hence identify or even quantify the material present in the irradiated sample. This is called **neutron activation analysis.** In the case we are interested in, the neutron irradiation is used to create radionuclides for radiopharmaceutical production. The parameters that control the amount of radioactivity produced are shown in equation 1.

$$A(t) = \sigma\phi N (1 - e^{-0.693t/T_{\frac{1}{2}}}) \tag{1}$$

t = time of irradiation
A = activity produced in disintegrations/second
σ = activation cross section
N = number of nuclei of a certain type presented to neutron beam
ϕ = flux of neutrons in neutrons/cm²-sec
$T_{\frac{1}{2}}$ = half-life of material produced

N will be affected by the amount of enrichment that has been performed on the target material.

$$N = 6.023 \times 10^{23} \times \text{weight (gram)} \tag{2}$$
$$\times \frac{\text{abundance of isotope in question}}{\text{atomic weight}}$$

A neutron is added to a stable nucleus in reactor production. Hence, the atomic number does not change, and the atomic mass is increased by 1 in the general case. This produces neutron-rich nuclides that usually decay by emitting a beta or alpha particle. We are interested only in the beta emitters, which may also have some gamma rays. Ideally, we use the activated material as a precursor to some gamma emitting material so that we do not have to inject the beta emitter into the patient; ^{99m}Tc is a nuclide produced in such a fashion. ^{98}Mo

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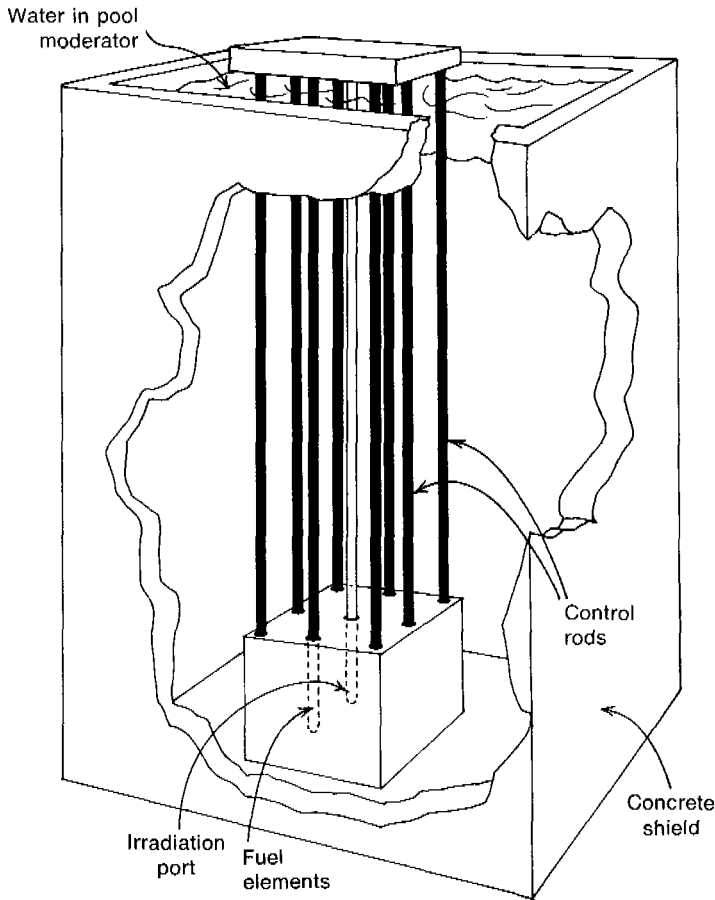
Fig. 8-1. Swimming-pool type of nuclear reactor. Solid rods are used to control rate of neutron multiplication. Hollow rod is for insertion of sample into core for neutron irradiation.

forms 23.78% of natural molybdenum. Molybdenum irradiated for 1 week at a flux of 2×10^{14} n/cm²-sec yields 1 Ci of ^{99}Mo.

SEPARATION TECHNIQUES

$$A_i(t) = \sigma_i \phi_i N_i (1 - e^{-0.693t/T_{\frac{1}{2}i}}) \qquad (3)$$

This equation (which is very similar to the preceding one, except it has lots of *i*'s in it) means that the same equation holds for every species in the sample that has been irradiated. Therefore, if you wish to have a pure product, it helps to enrich the target in the material of primary interest. One can obtain up to a 99% enrichment of ^{98}Mo. High enrichment is better for irradiation. Most important, the impurities that

have high cross sections should be eliminated if possible. For example, there are traces of tungsten in natural molybdenum targets that lead to radioactive tungsten in the product. It is also possible to allow undesirable short-lived products to decay away before using the product. This is another way to improve radionuclidic purity.

Once the target has been irradiated and is ready for processing, it is, of course, very radioactive even after the ultrashort-lived nuclides have decayed away. The target is usually processed remotely by robot hands either behind lead glass or under TV control, so the operator is not irradiated. The target holder is removed and the chemical separation of the

target from its impurities performed so that the radionuclide is prepared in the desired chemical form. Precipitations are often used to separate the desired radionuclide from the impurities. Conversion to the gaseous state may be employed to effect a separation. Extraction of the product may involve chromatography or extraction in a liquid-liquid system. Sometimes, distillation can be used to separate the product from the impurities. Molybdenum targets are dissolved in ammonium hydroxide to form the molybdate ion that is adsorbed on the column from which we subsequently elute ^{99m}Tc.

SPECIFIC ACTIVITY

We have not suggested that the neutron activation process is able to turn all the atoms of target material into products. The flux of the reactor and the neutron cross section will determine that. Therefore, when the product is obtained, and when there has been no change in chemical identity, it will not be possible to separate the unreacted target nuclei from the radioactive product nuclei by chemical means. The unchanged target material is called *carrier* because it carries the trace quantities of radioactive nuclei through the chemical separation steps. **Specific activity** is the term describing the number of millicuries produced compared to the number of milligrams of the element present. A higher neutron flux for the irradiation will produce a higher specific activity in the product.

The Szilard-Chalmers reaction can sometimes be used to increase specific activity. When a nucleus accepts a neutron, a prompt gamma ray is emitted, releasing the excess nuclear energy. The atom's nucleus recoils with the release of this gamma ray. The recoil energy can effect chemical changes such that the radioactivated nuclei are converted into a different chemical species. This alteration of chemical state allows us to separate the radioactive isotope from the nonradioactive isotope. An example of this is the production of ^{128}I$^-$ by the thermal neutron irradiation of ethyl iodide. The prompt gamma recoil that occurs as the ^{127}I is converted to ^{128}I ruptures the carbon-iodine bond and permits the subsequent use of simple chemical techniques to separate the two

isotopes. When NaI is used as target material for the irradiation, both isotopes exist as the same chemical species and are inseparable. Thus, the irradiation of ethyl iodide can be used to produce a higher specific activity of the product radioiodine.

EXAMPLE: ^{18}F FROM LiCO$_3$

We have previously referred to molybdenum 99 production as an example of radioisotope production. It is typical of productions where the product is identical chemically to the target. Fluorine 18 is produced by a more complex set of reactions in the reactor that illustrate the possibilities for such processes. One starts with a target of lithium-7 carbonate, and the reactions are:

$$^7\text{Li (n, }\alpha\text{) }^3\text{H} \quad or \quad {}^7\text{Li} + \text{n} \rightarrow {}^3\text{H} + {}^4\text{He}$$
$$\text{and}$$
$$^{16}\text{O (t, n) }^{18}\text{F} \quad or \quad {}^{16}\text{O} + {}^3\text{H} \rightarrow {}^{18}\text{F} + \text{n}$$
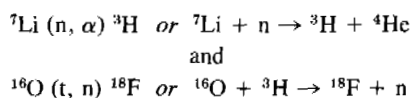
When ^{18}F is produced by this method, the tritium (^{3}H) also produced must be rigorously removed, since it has a long half-life and therefore can be responsible for significant patient radiation exposure. The material does not have to meet rigorous specifications otherwise, since it can be administered by mouth for bone scanning.

Linear accelerator and cyclotron production

Another way to make radioactive nuclei is to bombard stable nuclei with charged particles, such as electrons, protrons, and deuterons. This may be done by accelerating ions along a linear path using an electric current for acceleration and voltage for control. The machine for doing this is a linear accelerator (Fig. 8-2). Alternately, a beam of charged particles may be produced by accelerating ions around in a widening circle using a magnetic field for control and electric current for acceleration. The machine for doing this is a cyclotron (Fig. 8-3). At the outside of the circle the particles are sent against a target. The current and the magnetic fields determine the focus and the energy to which the particles will be accelerated. It is necessary to accelerate charged particles to provide them with sufficient energy to overcome
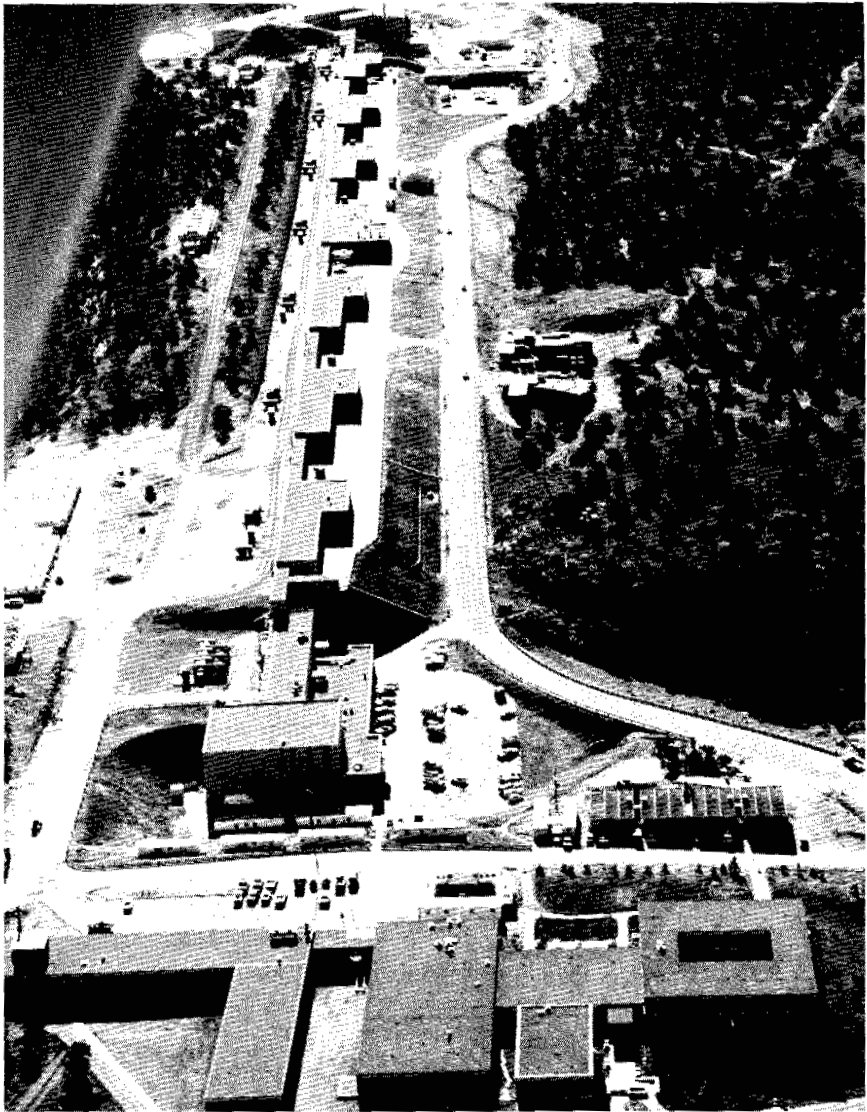
Fig. 8-2. Aerial view of LAMPF, accelerator at Los Alamos, New Mexico.

the barrier surrounding the nucleus. This barrier repels the particles that do not have the energy required for penetration. The cyclotron equation is:

$$E = \frac{r^2 H^2 e^2}{2M} \qquad (4)$$

where E = energy produced
 r = circle radius
 H = magnetic field strength
 e = electronic charge
 M = rest mass of particle

When the velocity approaches that of light, the mass rises. This can be compensated by field changes or by the shaping of the magnets. Usually, it is the positively charged particles that are accelerated.

Again, greater product specificity can be achieved by purifying the target materials before irradiation and by using the same types of product preparations as in reactor production. There are many more alternative routes for achieving the same product. For instance, when
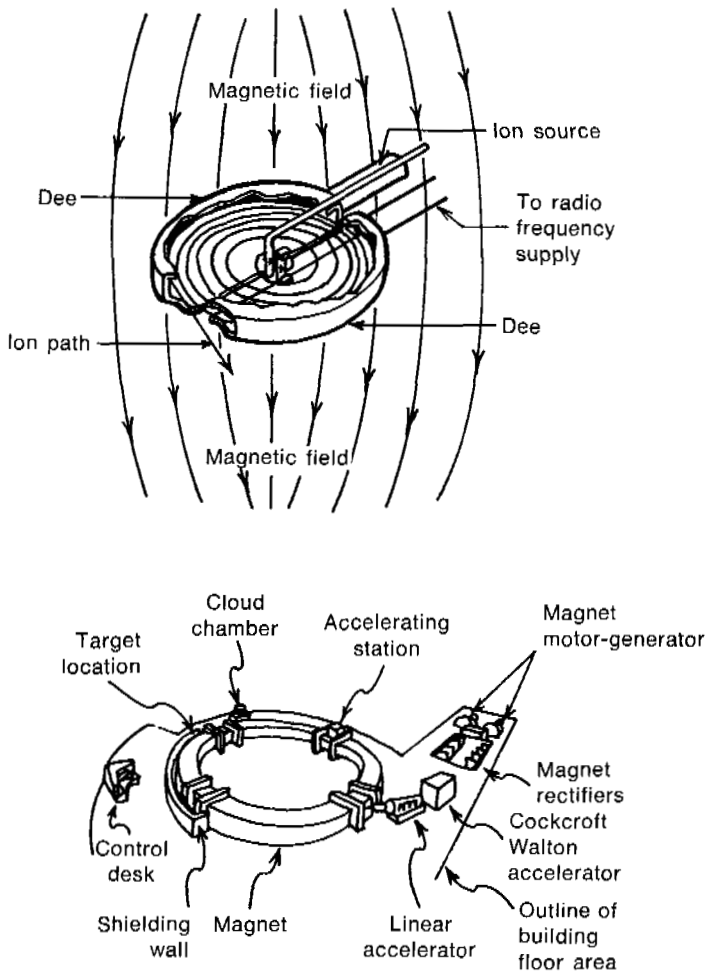
Fig. 8-3. Schematic of cyclotron.

Table 8-1. Positron-emitting tracers of C, N, and O

Isotope	$T_{1/2}$	Radiation	Production	Compounds
^{11}C	20.4 min	β^+	$^{10}B\ (d,\ n)\ ^{11}C$	^{11}CO, $^{11}CO_2$, fatty acids, glucose, $^{11}CN^-$
^{13}N	9.96 min	β^+	$^{12}C\ (d,\ n)\ ^{13}N$	$^{13}NH_3$, $C^{13}N^-$, glutamic acid
^{15}O	2.05 min	β^+	$^{14}N\ (d,\ n)\ ^{15}O$	$O^{15}O$, $C^{15}O$, $H_2^{15}O$
			$^{16}O\ (p,\ pn)\ ^{15}O$	
			$^{12}C\ (\alpha,\ n)\ ^{15}O$	

a proton enters the nucleus at one energy, one set of products emerges. When another energy is used, another set of products emerges. In all cases the chemical identity of the target and product will *not* be the same, so the product element will be a different element than the starting material. This means the product is **carrier free,** which may have advantages when its use is considered. Competing reactions, however, may produce a whole battery of radioactive products, so energy and target selection are important. The products will in general

¹¹CO carboxyhemoglobin
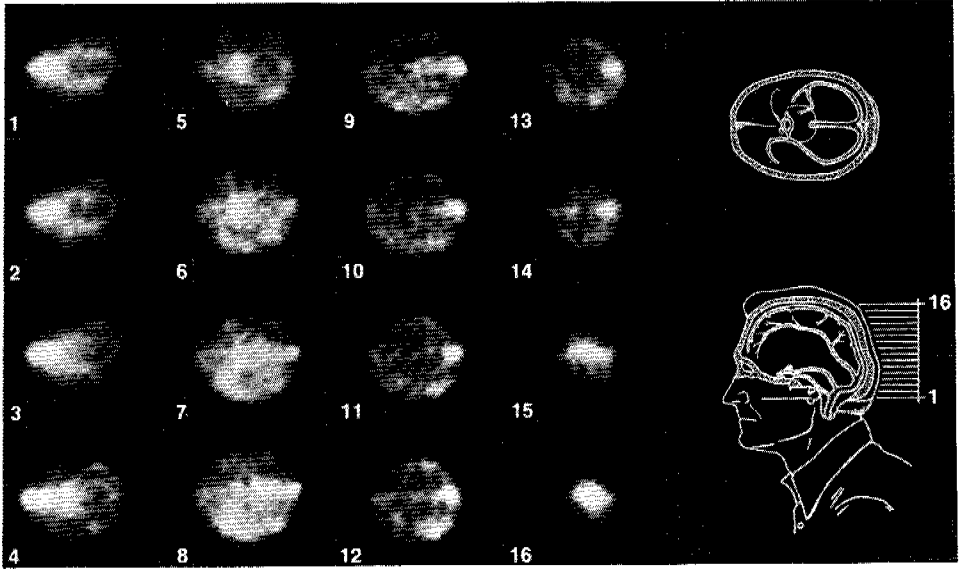
Fig. 8-4. Positron tomograms of head with ¹¹CO as radiopharmaceutical. (Courtesy Washington University School of Medicine, St. Louis, Mo.)
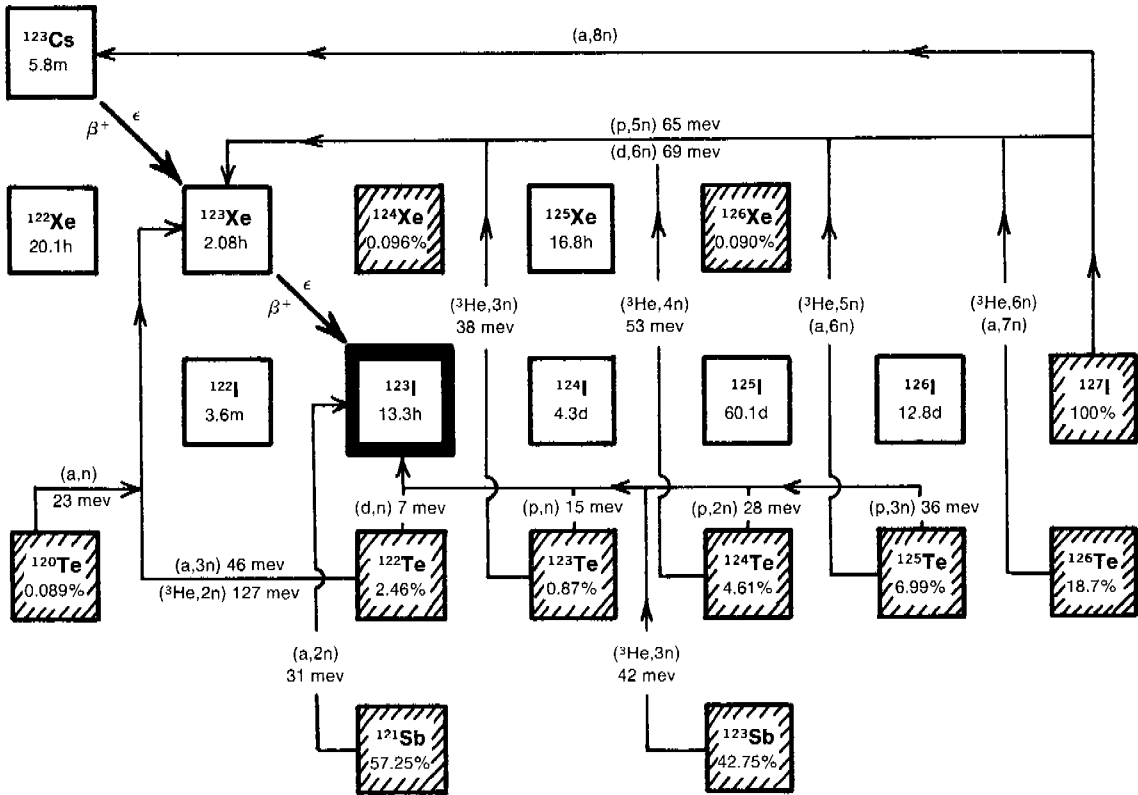
Fig. 8-5. ¹²³I can be produced from many different combinations of nuclear reactions and radioactive decay schemes.

Cyclotron-produced nuclides

^{57}Co is produced from ^{60}Ni(p,α)^{57}Co for long-lived sources of energy close to ^{99m}Tc and for the Schilling test.

^{67}Ga is produced by one of several reactions starting with ^{60}Zn, ^{67}Zn, ^{68}Zn, or ^{65}Cu and is used for tumor and abscess localization and appears to be carried on iron-binding sites.

^{111}In is produced from ^{109}Ag(α,2n)^{111}In, which is used as ^{111}In chloride and in bone marrow imaging and ^{111}In DTPA that has been used for CSF studies.

^{201}Tl is produced from ^{203}Tl(p,3n)^{201}Pb $\xrightarrow[9.4\,h]{}$ ^{201}Tl for an analog tracer of potassium, used primarily for imaging the normal myocardium.

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have an excess of protons over neutrons in their nuclei and will tend to decay by electron capture and/or positron decay.

^{11}C, ^{13}N, ^{15}O

Table 8-1 shows the most widely applicable positron emitters. Their half-lives are short, and the positron radiation is not easy to collimate. If one has a positron camera near a cyclotron, these are exciting nuclides to work with. The short half-lives allow repeated or complementary studies, such as imaging the blood flow with ^{11}CO and the heart muscle with ^{13}NH$_3$. There are several positron-computed axial tomography instruments in use that can visualize these nuclides in three dimensions (Fig. 8-4).

HALOGENS (^{123}I AS AN EXAMPLE)

Iodine 123, with a half-life of 13.3 hours and a principal gamma-ray energy of 159 kev, is a very promising nuclide. There are many pathways to it, depending on the starting materials and the accelerator beam. Fig. 8-5 shows the possibilities.

The two general methods are (1) direct reaction or (2) preparing ^{123}Xe, then allowing the ^{123}Xe to decay into ^{123}I. This second method avoids the ^{124}I impurity, but not the ^{125}I impurity. The direct methods usually yield a product with ^{124}I contamination. ^{124}I is a problem because it increases in relative concentration and limits the shelf-life to 4 days. Another problem with ^{124}I contamination is its positron annihilation radiation and its other high-energy gammas that cannot be collimated out very well. These radiations contribute to image fuzziness. ^{125}I is long lived (60 days) with low-

Table 8-2. Comparison of reactor and accelerator production of isotopes

	Production method	
	Reactor	**Accelerator**
Bombarding product	Thermal n	p, d, t, α
Kind of product	Neutron rich	Proton rich
Kind of decay path	β^-	β^+, EC
Comment	Carrier present	Other carrier free

energy emissions (27 kev, 35 kev); these emissions do not degrade the image, but the long half-life means a higher radiation dose when it is administered as a contaminant of ^{123}I.

OTHER CYCLOTRON-PRODUCED NUCLIDES

The most widely used of the cyclotron-produced nuclides are ^{57}Co, ^{67}Ga, ^{111}In, and ^{201}Tl. Production and use of these as diagnostic tracers are summarized above.

Table 8-2 compares the two major methods for preparing radionuclides.

Fission production

The high-atomic–weight nuclei of atomic number 92 and above are capable of fission or breaking apart, giving off neutrons and two lower-atomic–number products. ^{235}U is the most common of these fissioning nuclei. The products can be collected and separated by chemical means. ^{99}Mo, for example, can be extracted from fission products in curie quantities with high specific activity and used to make ^{99m}Tc generators with high specific activity. ^{131}I is also a fission product, as are ^{133}Xe and

[3]H. These last three are unavoidable fission by-products and, because they are volatile, can present reactor radiation safety problems.

Suggested readings

Friedlander, G., and Kennedy, J. W.: Nuclear and radio-chemistry, ed. 2, New York, 1964, John Wiley & Sons, Inc.

International Atomic Energy Agency: Radioisotope production and quality control, IAEA Technical Report Series No. 128, Vienna, 1971.

Koch, R. C.: Activation analysis handbook, New York, 1960, Academic Press, Inc.

National Bureau of Standards: A manual of radioactivity procedures, Handbook 80, U.S. Department of Commerce, Washington, D.C., 1961, U.S. Government Printing Office.

Generator systems

General characteristics

The study of parent radionuclides and their relationships to their daughters is as old as the knowledge of radioactivity. Radon 222 gas separates from its parent, radium 226, because it is a gas (Fig. 9-1). The ^{226}Ra provides a simple source of ^{222}Rn; this system is still in use today. The National Bureau of Standards sells calibrated quantities of ^{226}RaCl$_2$, which can be made up in an airtight system to generate ^{222}Rn as a standard for alpha counting. This illustrates the use of a *generator,* which is a parent-daughter combination designed to yield the daughter for some purpose that is usually separate from the parent. The reason for our employing such a system, that is, for having the parent nuclide in our laboratories, is that the important daughter nuclides have short half-lives compared to the travel time from the manufacturer to us. To be useful, the parent's half-life must be long, compared to the travel time. In the modern world there are many differences in transportation and in the time it takes to travel a few thousand miles. Thus, it is necessary to use parent nuclides with half-lives of several months in some parts of the world, whereas parent nuclides with half-lives of less than 3 days are satisfactory for other regions. In some regions it is possible to ship daughter nuclides directly, even when the daughter's half-life is only 6 hours. Thus, there are many areas of the United States where ^{99m}Tc can be separated by a radiopharmacy and shipped directly to the user.

Daughter nuclides from generators must fulfill essential characteristics to make them suitable for biomedical applications. The daughter must have different chemical properties from the parent; usually, this occurs because the daughter differs by 1 in atomic number from the parent and is therefore a different element. The differences in chemical properties are used to effect a chemical separation between the two. Usually, the separation occurs chromatographically. The parent is absorbed on a chromatograph column and remains there while the daughter is eluted with a suitable eluant. The vocabulary used is that of chromatography, in which the original separations and observations were made on moving color bands. (For a practical example of chromatography, put spots of pen ink on a napkin or tissue. Dip a corner of the paper into water and allow the water to be picked up and flow past the ink spots. Observe the separation of the colors. This is chromatography.)

In addition to chemical properties that permit easy separation of the parent and daughter radionuclides, the chemistry of the daughter nuclide should also permit its rapid formulation into radiopharmaceuticals that can be used in clinical nuclear medicine. Usually, this means that reagent kits in a closed preparation procedure can be developed to **compound** the radiopharmaceutical on short order. The research that goes into creating these kits may take several years. The pharmaceuticals often go through many phases of development, becoming simpler to use at each reformulation.

The generator system permits a constant supply of the daughter nuclide. Properties of an ideal generator are listed on p. 114. The use of kits with generator eluants permits the formulation of several compounds, allowing us to adjust to meet day-by-day variations in demand. The demand depends on the patient examination

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Fig. 9-1. Radon 222 generator.
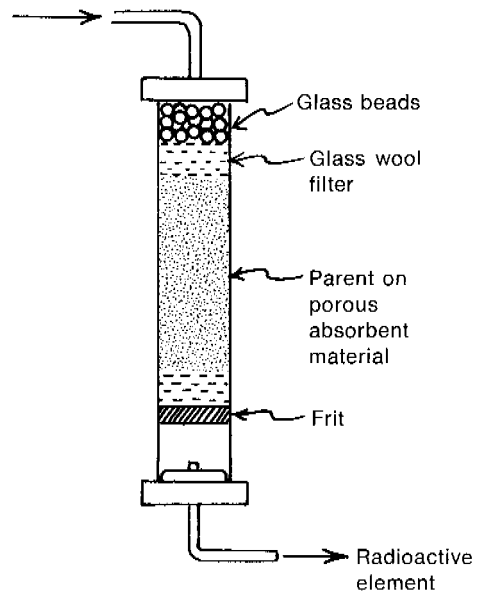
Fig. 9-2. Chromatograph-column type of generator, such as is used for separation of ^{99m}Tc from ^{99}Mo.

load. Thus, it is more economical to use generators and kits than it is to stock a sufficient supply to meet high demand periods. In this latter situation, the quantity of each material that radioactively decays away to nothing without ever having been used is excessive.

Construction

Generators have been made in several ways, depending on important chemical differences between the parent and daughter nuclides. The chromatograph column has come to be the most widely used system because of its ease of operation. It can be remotely controlled with excellent reproducibility. Systems for shielding, packaging, and transport of column generators are currently well worked out.

Fig. 9-2 shows a diagram of a typical column generator. The model column is a glass tube, closed at either end with stoppers. The glass tube contains, in the order the liquid flows through, a disk with holes in it or a piece of **fritted glass,** often backed up by glass wool to spread out the entering liquid evenly and to

keep the column material in place during shipping; the column material itself, with the parent nuclide adsorbed on it in the proper chemical form; a piece of fritted glass for the liquid to exit through but which retains the column material; and very often, a filter to remove bacteria and any other debris before the outflow. Elution is accomplished by the eluant flowing through
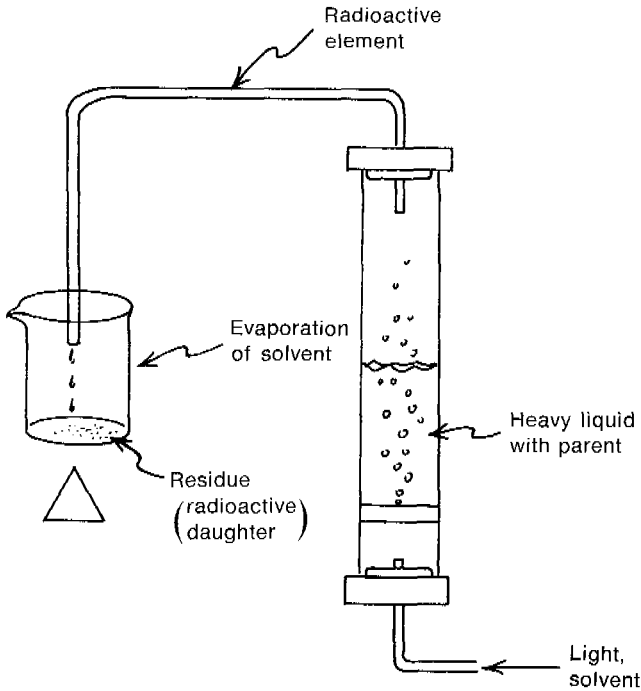
Fig. 9-3. Liquid-liquid extractor type of generator. This type of generator can be adapted for separation of ^{99m}Tc from ^{99}Mo with methylethyl ketone as extracting liquor.

the column. The source of eluant may be individual unit-elution bottles external to the generator or a bottle of eluant used for multiple elutions over a period of time, or it may be internally packed within the generator shielding. A vial is often evacuated to pull a given volume of eluant through the column. The whole elution process is usually enclosed with a system of tubing and needles to prevent contamination by microorganisms. Packing materials and lead shielding around the generator column keep it from being damaged during shipping and prevent radiation to the surroundings.

Other systems have been employed that do not use chromatograph columns. Liquid-liquid extraction can be used to effect the parent-daughter separation (Fig. 9-3). In general, this requires more manipulation than the solid generator, although it can be automated. Liquid-liquid extraction may permit very high concentration of the daughter when the solvent containing the extracted daughter nuclide is evaporated to dryness and then the radioactivity is dissolved

in minute volumes of saline. Other systems are based on distillation, **sublimation,** or gaseous diffusion to separate the daughter from the parent nuclide.

The generators are constructed in general to be sterile and pyrogen free. Because they are eluted many times throughout their life, they must be treated carefully to maintain this initial state. The elution vials and eluant solution are usually supplied by the manufacturer, but if they are not, care should be taken in their use. The ^{99m}Tc generator is usually eluted with bacteriostat-free saline because the oxidant qualities of the **bacteriostat** interfere with radiochemical reactions. Sterile, disposable supplies are used with generators. Sterilization can often be used in cases of suspected septic technique; however, this will not affect pyrogen contamination. Thus, extreme care must be exercised whenever the generator is in use.

Some generators can be reloaded. For example, rechargeable ^{99}Mo/^{99m}Tc generator systems are usually used when the demand for
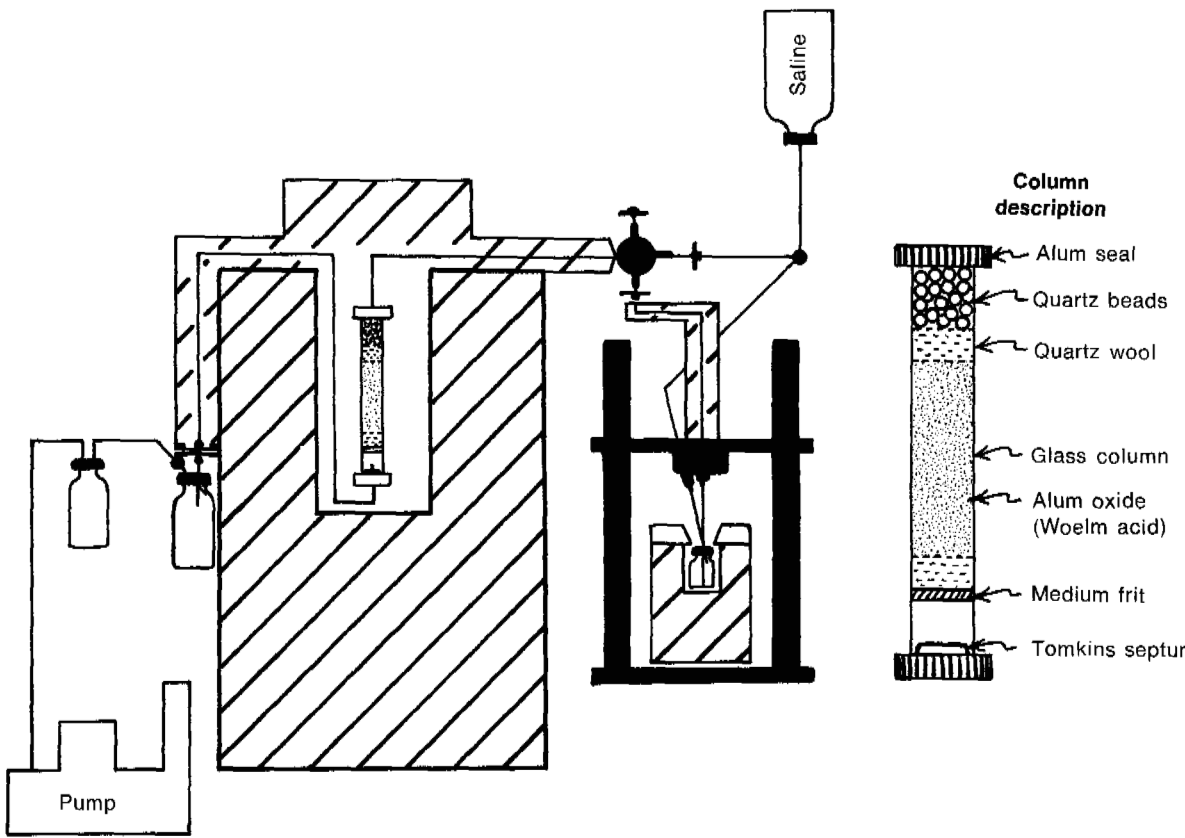
Fig. 9-4. Rechargeable generator suitable for repeated loading with ^{99}Mo.

^{99m}Tc begins to exceed a curie per day. Fig. 9-4 shows one such generator system.

Operation

The relationship of parent-daughter radioactivity in a generator is calculated with the decay constants for the two species, as shown here in equation 1:

$$N_d = N_p^0(e^{-\lambda_p t} - e^{-\lambda_d t}) + N_d^0 e^{-\lambda_d t} \qquad (1)$$

N_p^0 and N_d^0 denote the number of parent (p) atoms and number of daughter (d) atoms at the time of the last elution; t is the elapsed time since the last elution.

If we wish to express the results as radioactivity, equation 3 is used; it follows from equation 2, the definition of radioactivity.

$$A_d = \lambda_d N_d \text{ and } A_p = \lambda_p N_p \text{ or } N_p^0 = \frac{A_p^0}{\lambda_p} \qquad (2)$$

$$A_d = \frac{\lambda_d}{(\lambda_d - \lambda_p)} A_p^0(e^{-\lambda_p t} - e^{-\lambda_d t}) + A_d^0 e^{-\lambda_d t} \qquad (3)$$

A_d^0 = activity of daughter left in generator after last elution
λ_p = decay constant of parent
λ_d = decay constant of daughter
A_p^0 = activity of parent after last elution
t = time of last elution

In addition, if the daughter nuclide is only one of several products of the parent nuclide, the fraction of parent decaying through daughter of interest must be taken into account. Equation 4 is used for this situation:

$$A_d = \frac{\lambda_d}{\lambda_d - \lambda_p} f_{pd} A_p^0(e^{-\lambda_p t} - e^{-\lambda_d t}) + A_d^0 e^{-\lambda_d t} \qquad (4)$$

where f_{pd} = fraction of parent that decays to daughter in question

Often it is more useful to express these equations in terms of half-lives rather than decay constants. The two constants are related as shown in equation 5. Equation 6 is identical to equation 4 except for the substitution of constants.

$$\lambda = \frac{0.693}{T_{\frac{1}{2}}} \qquad (5)$$

$$A_d = \frac{T_p}{T_p - T_d} f_{pd} A_p^0 (e^{-0.693\ t/T_p} - \qquad (6)$$

$$e^{-0.693\ t/T_d}) + A_d^0 e^{-0.693\ t/T_d}$$

where T_p = half-life of parent
T_d = half-life of daughter

Several general cases describe the various relationships possible between parent and daughter radioactivities based on their relative half-lives. *Secular equilibrium* is the case where the parent half-life is many times greater than the daughter: $T_p \gg T_d$. Hence, after an elution the amount of parent radioactivity shows little change while the daughter radioactivity grows in. Radium 226 (T = 1,620 years) and radon 222 (T_d = 3.8 days) are typical of such a system. If the system is allowed to rest for many days (more than ten times the daughter half-life), the decay terms for the daughter radioactivity of the equation become negligible, and the equation simplifies to equation 7 or 8:

$$A_d = f_{pd} A_p^0 e^{-0.693\ t/T_p} \qquad (7)$$

or if $f_{pd} = 1$ (and $e^{-0.693\ t/T_p} \approx 1$)

$$A_d = A_p^0 \qquad (8)$$

The radioactivity of radon 222 eluted from a fully rested (regenerated) generator is equal to the radioactivity of radium 226 in the generator.

Transient equilibrium is the case where the half-life of the parent nuclide is greater than the daughter, but not by many times. The daughter's decay terms become small compared to that of the parent but enter into the calculation at less than four or five daughter half-lives. ^{99m}Tc from the ^{99}Mo/^{99m}Tc generator is an example of such a system. ^{99}Mo has a half-time of 67 hours, the fraction decaying to ^{99m}Tc is 0.92, and ^{99m}Tc has a half-life of 6 hours.

$$A_d(t) = \frac{67}{67 - 6} \times 0.92 \times A_p^0 (e^{-0.693\ t/67} - \qquad (9)$$

$$e^{-0.693\ t/6}) + A_d^0 e^{-0.693\ t/6}$$

where t is expressed in hours

Equation 9 allows the calculation of the amount of ^{99m}Tc radioactivity at any time after elution.

$$A_p^0(t) = A_p^0 e^{-0.693\ t/67} \qquad (10)$$

Equation 10 allows the calculation of the amount of ^{99}Mo remaining since the time of the *last* elution. As the time since the last elution grows long, the daughter's half-time becomes insignificant to the calculation. Thus, equation 9 simplifies to equation 11 or 12.

$$A_d(t) = \frac{T_p}{T_p - T_d} f_{pd} A_p^0 e^{-0.693\ t/T_p} \qquad (11)$$

where $A_p = A_p^0 e^{-0.693\ t/T_p}$ describes parent decay, so that

$$A_d(t) = \frac{T_p}{T_p - T_d} f_{pd} A_p \qquad (12)$$

There is *no equilibrium* if the daughter's half-life is longer than that of the parent's.

If the "granddaughter," or the product of daughter decay, is not stable, this set of equations governs that, too.

^{99}Mo/^{99m}Tc generator
DESCRIPTION

The arithmetic of the operation of a ^{99}Mo/^{99m}Tc generator has been described in equation 9. This generator system is one of the oldest in use in nuclear medicine and is still the best because of the nearly ideal properties of ^{99m}Tc. It does have a radioactive third-generation decay product, ^{99}Tc, but this has a long half-life ($T_{\frac{1}{2}} = 2 \times 10^5$ years). This means millicurie quantities of ^{99m}Tc create micromicrocurie amounts of the radioactive granddaughter of ^{99}Mo, that is, ^{99}Tc.

The most widely used ^{99m}Tc generator contains at its heart a glass or plastic cylinder filled with alumina (Al_2O_3), which is a common chromatograph column–packing material. The ^{99}Mo molybdate produced from the neutron-irradiated MoO_3 target is solubilized and then
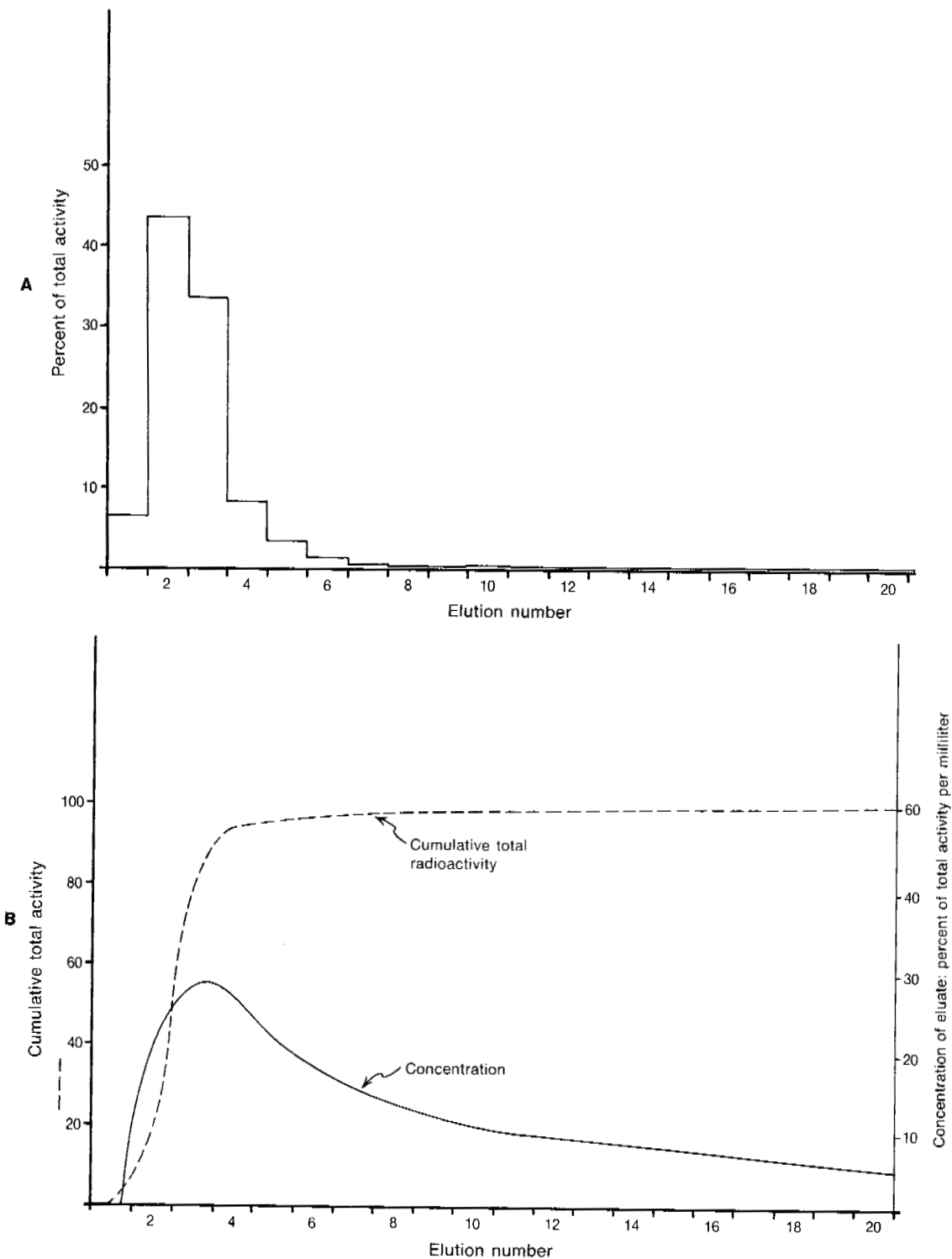
Fig. 9-5. A, Fractional elution histogram for 600 mCi New England Nuclear ^{99m}Tc generator (fission ^{99}Mo). Generator was eluted repeatedly with 1 ml aliquots of saline; radioactivity of each milliliter was measured. Data were normalized using total activity in 20 ml as 100%. **B,** Cumulative total radioactivity: running sums for elutions reported in histogram are plotted. Concentration: values for running cumulative total radioactivity are divided by cumulative volume.

put onto the column at pH 3. The column is thoroughly washed (with 0.9% saline) to remove unbound radioactivity and then packaged inside the generator. **Aseptic** techniques are used. To assure sterility, the generator is sterilized after preparation.

Elution is carried out by attaching a source of 0.9% saline (without bacteriostat) solution, which may be, as just explained, in individual vials, in an external bottle, or packed inside the shielding and permanently connected by tubing to the column. An evacuated vial of 5 to 30 ml volume is attached to the exit side. The saline flows from the saline source through the column and then into the evacuated vial. The volume of eluant is such that it exceeds the void volume of the column by several times. Fission ^{99}Mo has a very high specific activity and can be put onto small columns. The void volume is small; the elution volume is therefore small so that the product has a high concentration of ^{99m}Tc. Reactor ^{99}Mo contains carrier ^{98}Mo and therefore takes a larger volume column to absorb all the molybdate. This limits the concentration of the ^{99m}Tc eluate. The graph in Fig. 9-5 of radioactivity-eluted-versus-elution volume for a typical column shows that a large part of the activity comes through in the first few milliliters of eluant. Thus, in order to achieve higher concentration in the product, one may fractionally elute the column by stepwise flushing it with small elution volumes. For a generator whose normal elution volume is 20 to 30 ml, fractionation into 5 ml aliquots is satisfactory and is especially helpful when a part of the eluate is needed for tests requiring high concentrations of radioactivity.

An examination of the arithmetic of the ^{99}Mo/^{99m}Tc parent-daughter relationship shows that the daughter has grown in significantly after one daughter half-life. Thus, 6 hours after a previous elution, 50% of the maximum amount of ^{99m}Tc can be obtained by another elution. This effect, combined with fractional elution, makes it possible to achieve an almost constant supply of ^{99m}Tc of the required concentration.

Other methods for separating ^{99m}Tc from ^{99}Mo have been devised. The ^{99}Mo as molybdate is kept in a stock solution of 5N NaOH.

Methylethyl ketone (MEK) is added; MEK is not miscible with water. It forms a layer over the water. As the two liquids are shaken together, the ^{99m}TcO$_4^-$ dissolves in the MEK, removing it from the aqueous solution of ^{99}Mo. The two liquids are allowed to clear and separate. The MEK is evaporated. The residual ^{99m}Tc is reconstituted with 0.9% saline to any desired concentration. This system, which can be used to make ^{99m}Tc with a constant concentration every day, can be shielded, automated, and made to perform in a very reproducible fashion.

Another method of separation involves subliming Tc$_2$O$_7$ away from molybdenum that has been deposited on fritted glass. The system can be scaled up to multicurie sizes but has the disadvantages of high temperatures and high initial costs. The impurities are in extremely low quantity when this method is used.

EVALUATION OF ELUATE

The technetium 99m comes from the generator as ^{99m}TcO$_4^-$, a highly soluble product. There is, of course, some carrier ^{99}TcO$_4^-$ present as well because all ^{99m}Tc decay leads to ^{99}Tc, as does the other 8% of ^{99}Mo that does not decay through ^{99m}Tc metastable state. Thus, every molybdenum atom that has decayed since the last elution of the generator is converted into either ^{99m}Tc or ^{99}Tc.

The 0.9% saline solution used to elute the generator should be essentially unchanged from when it went into the generator. The added ^{99m}Tc amounts to all of about 2×10^{-8} grams of ^{99m}TcO$_4^-$ and perhaps 5×10^{-8} grams of ^{99}TcO$_4^-$ for every 100 mCi of ^{99}Mo that was present 24 hours previously. The saline may be chemically and radionuclidically contaminated in several ways. It is possible for some ^{98}Mo (from reactor ^{99}Mo preparation) and alumina to appear in the eluate. It is also possible for ^{99}Mo to appear, along with products of irradiation of molybdenum contaminants, such as ^{103}Ru, ^{132}Te, ^{131}I, and ^{132}I (a ^{132}Te decay product). Under usual circumstances only the ^{99}Mo contaminant is large enough to be detected by the tests performed routinely on generator eluate. A solid-state, gamma-ray detector such as Ge(Li) can detect these and other gamma radioactive

impurities in small amounts. If the elution products are saved and the ^{99m}Tc allowed to decay, a study may be made of the impurities by a Ge(Li) detector with multichannel spectral analysis (Fig. 9-6). ^{134}Cs, ^{131}I, ^{239}Np, ^{103}Ru, ^{86}Rb, ^{60}Co, and ^{124}Sb are the major impurities. If generator columns are saved for many months and the ^{99}Mo allowed to decay away, the impurities in the molybdenum can be studied; ^{134}Cs, ^{124}Sb, ^{95}Zr, and daughters ^{65}Zn and ^{60}Co have been found. The MEK extraction method produces a cleaner eluate, as does the sublimation method.

The generator may be subject to self-radiolysis by its contents. This problem is particularly acute in fission ^{99}Mo generators. The result is that all contents are subject to attack by **free radicals,** especially if there is liquid water present in the system. The free radicals may cause alumina breakdown or produce reduced

species of technetium that cannot be eluted. Keeping the generator dry after each elution helps minimize this effect.

There are several causes for decreased yield in generators:

1. Self-radiolysis leading to reduced ^{99m}Tc species
2. ^{99m}TcO$_4^-$ cannot get to the surface to be eluted
3. **Channeling** of eluant in the column so that not all the column is exposed to eluant
4. Other column factors

Since generators differ slightly in the details of construction and maintenance, we recommend that you read the package insert of your generator and use it according to the manufacturer's instructions. Generators are not particularly delicate, but they can be ruined by improper use.
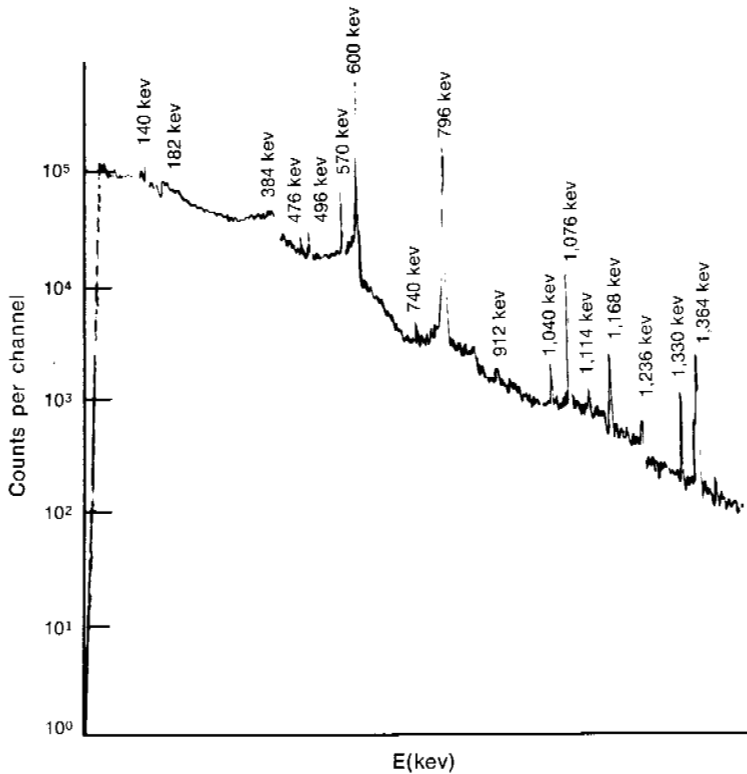
Fig. 9-6. Gamma-ray spectra of ^{99m}Tc eluate made after ^{99m}Tc radioactivity has decayed so that long-lived trace-radioactive impurities can be determined. (From Colombetti, L. G.: Performance of ^{99m}Tc generating systems. In Rhodes, B. A., editor: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.)

^{113}Sn/^{113m}In generator

DESCRIPTION

^{113m}In ($T_{\frac{1}{2}}$ = 1.6 hours, gamma-ray energy = 393 kev) can be made from a tin 113/indium 113m generator system. The ^{113}Sn has a half-life of 118 days, which means it need only be replaced every 6 months. Kit recipes are available for the preparation of various radiopharmaceuticals, so that ^{113m}In can be almost as versatile as ^{99m}Tc. Kits for the preparation of ^{99m}Tc radiopharmaceuticals may be adapted for use with indium. The energy is perhaps a bit high for the Anger camera, but it is very satisfactory for the rectilinear scanner.

EVALUATION OF ELUATE

The column material is zirconium oxide. Reactor-produced ^{113}Sn is applied to the column in HCl solution in its most highly oxidized (stannic, +4) state. The column is eluted with 0.05 N HCl. In 24 hours this column can be eluted for up to 100 mCi of ^{113m}In for each 100 mCi of ^{113}Sn. The ^{113}Sn cannot be easily de-tected in the presence of the ^{113m}In eluate. To test for ^{113}Sn breakthrough, the leftover eluate is saved for 24 hours. The next day, any ^{113m}In present in the 24-hour-old eluate must have come from breakthrough ^{113}Sn in the vial, since all the original ^{113}In should have decayed away by then. Chemical impurities can include zirconium oxide and stable tin, which can be tested for. Radionuclidic impurities may include tin and antimony nuclides that have long half-lives.

Generators for ultrashort-lived nuclides

USES

Generators whose products have half-lives in the seconds and minutes range have been used for examinations taking place rapidly or as constant infusions. One can imagine the generator connected between an IV bottle and the patient's arm for a constant infusion (Fig. 9-7). At least one system has a gaseous product that can be used in rebreathing fashion. The advantage of the ultrashort half-life is the large
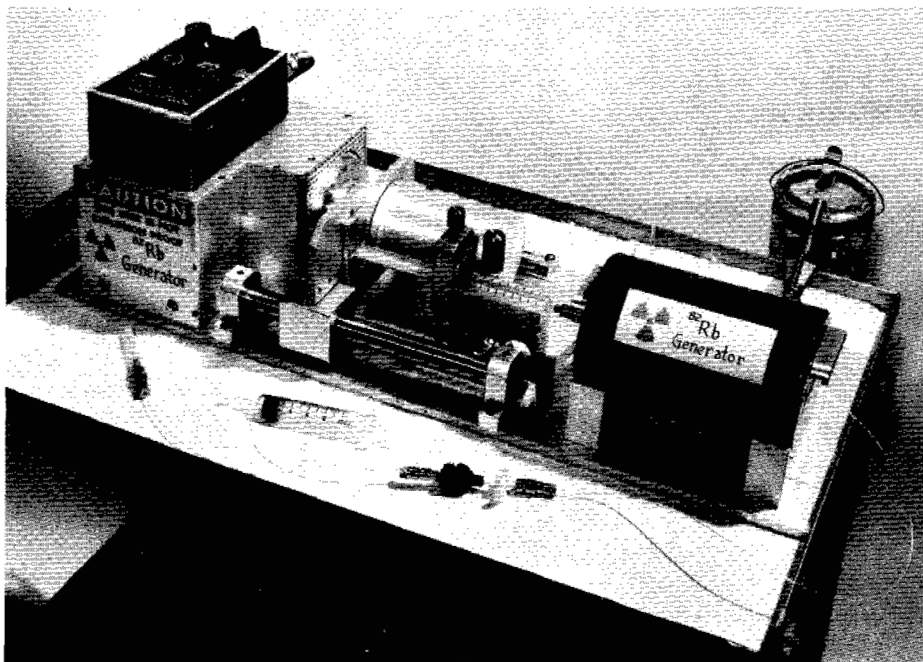
Fig. 9-7. Rubidium 82 generator that delivers radioactive tracer directly into an IV catheter. (From Budinger, T. F., Yano, Y., and Hoop, B.: J. Nucl. Med. **16:**429-431, 1975; courtesy Donner Laboratory, Berkeley, Calif.)

Nuclide generators used to produce radiopharmaceuticals

$$^{62}Zn \xrightarrow[9.8h]{\beta^+, \epsilon, \gamma} \rightarrow {}^{62}Cu \xrightarrow[9.2m]{\beta^+ \gamma} \rightarrow {}^{62}Ni$$

$$^{68}Ge \xrightarrow[275d]{\epsilon} \rightarrow {}^{68}Ga \xrightarrow[1.14h]{\beta^+, \epsilon, \gamma} \rightarrow {}^{68}Zn$$

$$^{81}Rb \xrightarrow[4.7h]{\beta^+, \epsilon} \rightarrow {}^{81m}Kr \xrightarrow[13s]{\gamma} \rightarrow {}^{81}Kr$$

$$^{82}Sr \xrightarrow[25d]{\epsilon} \rightarrow {}^{82}Rb \xrightarrow[75s]{\beta^+, \epsilon, \gamma} \rightarrow {}^{82}Kr$$

$$^{99}Mo \xrightarrow[64h]{\beta^-, \gamma} \rightarrow {}^{99m}Tc \xrightarrow[6h]{\gamma} \rightarrow {}^{99m}Tc$$

$$^{113}Sn \xrightarrow[118d]{\epsilon} \rightarrow {}^{113m}In \xrightarrow[1.7h]{\gamma} \rightarrow {}^{113m}In$$

$$^{123}Xe \xrightarrow[2h]{\beta^+, \epsilon, \gamma} \rightarrow {}^{123}I \xrightarrow[13.3h]{\epsilon, \gamma} \rightarrow {}^{123}Te$$

$$^{132}Te \xrightarrow[3.24d]{\beta^-, \gamma} \rightarrow {}^{132}I \xrightarrow[2.26h]{\beta^-, \gamma} \rightarrow {}^{132}Xe$$

$$^{137}Cs \xrightarrow[30y]{\beta^-} \rightarrow {}^{137m}Ba \xrightarrow[2.55m]{\gamma} \rightarrow {}^{137}Ba$$

$$^{141}Os \xrightarrow[15d]{\beta^-, \gamma} \rightarrow {}^{191m}Ir \xrightarrow[4.9s]{\gamma} \rightarrow {}^{191}Ir$$
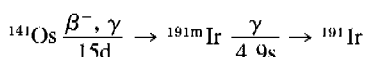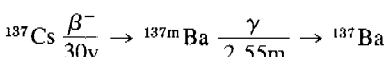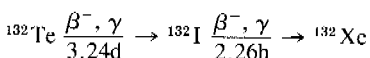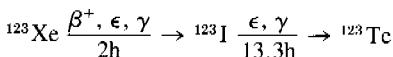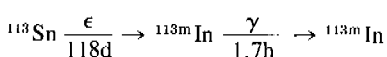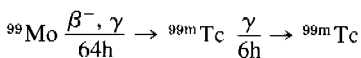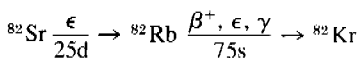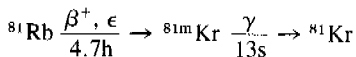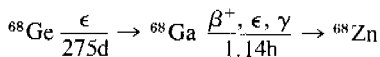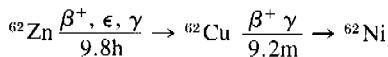
amount of radioactivity that can be used. This leads to very satisfactory count rates and permits rapid sequential studies.

EXAMPLES: $^{137}Cs/^{137m}Ba$, $^{81}Rb/^{81m}Kr$, and $^{82}Sr/^{82}Rb$

The 30 year–^{137}Cs/2.6 minute–^{137m}Ba system is interesting. For most purposes in nuclear medicine this combination is kept together and used as a standard source of 662 kev gamma rays for instrument calibration. The 662 kev gamma ray actually belongs to the ^{137m}Ba. The separation can be accomplished by flowing 0.1N HCl through a column of resin-asbestos, followed by an anti-^{137}Cs cartridge of ammonium phosphomolybdate. A commercial generator of this type is available, but not for human use.

The $^{81}Rb/^{81m}Kr$ generator has a short-lived (4.7 hours) parent and a very short-lived daughter, ^{81m}Kr ($T_{\frac{1}{2}} = 13$ seconds with a 190 kev gamma ray). The short physical half-life means that the radiation dose is low, so large quantities can be used for ventilation studies in place of ^{133}Xe. This material is currently in use in several institutions. ^{81}Rb is cyclotron produced from sodium bromide that is dissolved in a water solution. Air is bubbled through to remove the ^{81m}Kr.

The $^{82}Sr/^{82}Rb$ generator is currently being tested in several institutions. The parent ^{82}Sr has a half-life of 25 days, and the daughter ^{82}Rb has a half-life of 75 seconds. The ^{82}Rb is a positron emitter being tested as a myocardial imaging agent.

The accelerator-produced ^{82}Sr is adsorbed on an ion-exchange column and eluted with concentrated sodium chloride solution. The quality control procedures are conducted after the ^{82}Rb has decayed away, so high standards must be adhered to in storing and in eluting the columns.

Several decay schemes that are the basis of generators of importance in radiopharmacy are listed on the left.

Suggested readings

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Production of radiochemicals

Basic concepts

The subject of production of radiochemicals is much larger than nuclear medicine because the labeled compounds are widely created and used in chemical, biologic, biomedical, and biochemical research as well as in the clinical pathology laboratory. Thus, research radiopharmacists keep an eye on developments in many fields in order to take advantage of the findings in these fields to improve nuclear medicine.

Most labeled compounds are **organic** (there are more organic compounds to start with), and most of the currently available radiolabels are ^{14}C and ^3H, with a peppering of ^{32}P- and ^{35}S-labeled compounds. These are all beta emitters. These tracers are used primarily in tracer studies that do not involve human subjects. The analysis for the radioactivity is accomplished with liquid scintillation counting techniques. Liquid scintillation counting has evolved to the point that it is handy for almost any application.

The practice of nuclear medicine primarily requires gamma-emitting nuclides, and, as we have seen in Chapter 4, we are therefore somewhat limited to elements 20 through 83. Many of these elements are **metals,** so the labeling techniques in use in nuclear medicine are often somewhat different from those used for other applications. We shall concentrate here on the methods and elements that are most useful for nuclear medicine studies. These will be tagging with iodine, technetium and other metals, and syntheses for the incorporation of the positron emitters: ^{11}C, ^{13}N, and ^{15}O. We shall make little mention of nuclides used in their simple ionic forms, such as $^{22}Na^+$, $^{42}K^+$, and $^{51}CrO_4^=$, because these forms are stable and do not require synthetic methods.

Radioiodination

There are 24 radioactive isotopes of iodine; this is close to the largest number for any element. They are evenly spread on either side of the one stable isotope of iodine, ^{127}I. Of these, ^{123}I (13.3 hours, 159 kev), ^{125}I (60 days, 28, 35 kev), and ^{131}I (8 days, 364 kev) are in common use, while ^{132}I (2.3 hours, 760 kev) was used more in the past; ^{124}I (4.2 days, $\beta+$) has possible uses.

Iodine is a halogen. It exists in the elemental form as a gray-purple, shiny, nonmetallic solid that sublimes easily and is not very soluble in water. All nonelemental forms of iodine can be returned to I_2 by heat and light. Since elemental radioiodine will evaporate from the liquid phase, iodinations can create a radiation safety problem because of airborne contamination. The thyroid's great affinity for iodine will lead to a concentration of the radioiodine contaminants. Thus, iodine should be handled in radioisotope hoods to prevent personnel exposure during radioiodination reactions.

Several methods are in use for the iodination of large organic materials. A common thread running through the discussion of all these methods is the balance of the severity of the reaction conditions against the required specific activity of the radioiodinated product. To get the highest radiochemical yields, large amounts of the reactants can be used together with a reductant that will completely reduce all the iodide to iodine. However, severe reaction conditions can damage the molecule that is to be labeled or can lead to side reactions producing unwanted radiochemical impurities such as dimerized proteins. Severe conditions can also lead to uncertainty as to the position and num-

ber of iodines per labeled molecule. On the other hand, low specific activity often follows the use of mild conditions unless special techniques are employed and very high–specific activity iodine is used. For most applications a high specific activity is a requirement that must be met for the material to be useful.

One of the most useful methods for labeling proteins is an enzymatic method using lactoperoxidase to catalyze the oxidation of iodine by H_2O_2. The materials are mixed and flowed through a chromatography column (Fig. 10-1). The resulting iodinated product has the radio-iodine attached to the tyrosine of the protein. Radiolabeled proteins of high specific activity are created for radioimmunoassay; ^{125}I is usually the isotope of choice for these radio-iodinations.

The chloramine T (*N*-chloro-*p*-toluene sulfonamide) method oxidizes iodide into reactive species under somewhat severe conditions. All of the radioactive iodine is incorporated, producing a high–specific activity product; the product may be damaged, even if chloramine T concentrations are limited carefully and especially when the reaction time is prolonged. Several methods require reaction times of less than a minute (Fig. 10-2). There is little control over the level of substitution per labeled species.

Excitation, or recoil, labeling can be performed under certain circumstances. When the parent of one of the isotopes of iodine decays to iodine, the newly created nuclide, because of the recoil energy, is a species that is quite chemically reactive. As such, it will form stable chemical bonds with many types of molecules. For example, ^{123}I produced by the decay of ^{123}Xe can be used to label proteins and other molecules directly. When ^{123}Xe decays to ^{123}I in the presence of Cl_2, ICl is produced. The ICl has high specific activity and is an excellent reagent for radioiodinations (Fig. 10-3). If recoil labeling is used with larger species, there may be problems of damage and low specific activity of the product.
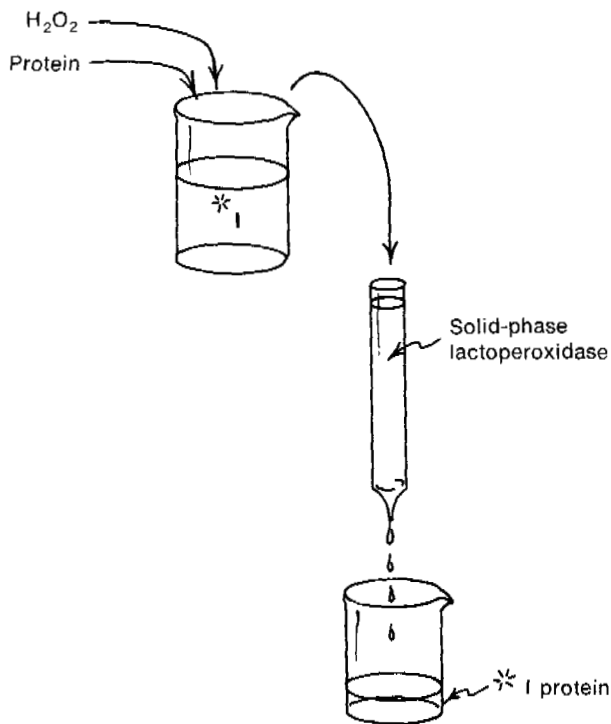
Fig. 10-1. Schematic procedure for radioiodination employing solid-phase lactoperoxidase.
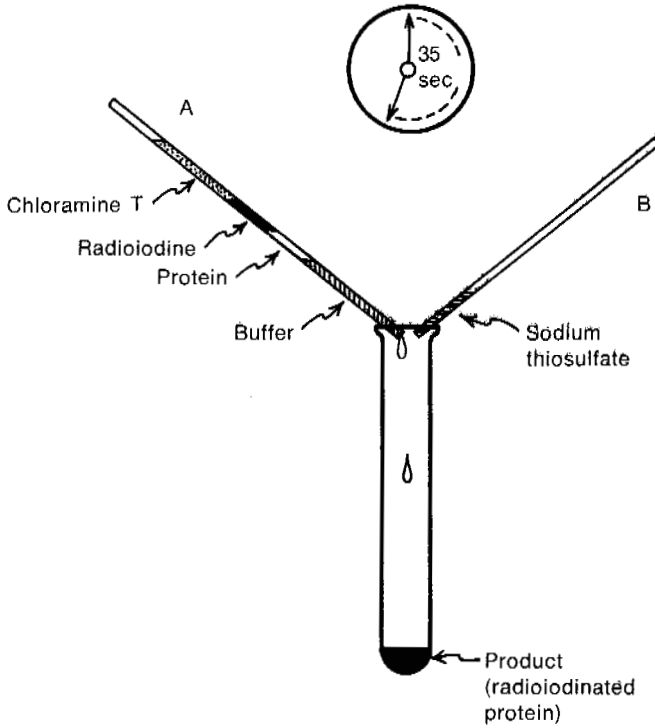
Fig. 10-2. Radioiodination of protein with microliter quantities of reagents and chloramine T. Micropipette *A* contains 20 μl of 0.1 m barbital buffer, pH 8.4, 5 μl (5 μg) of human growth hormone, 5 μl of carrier-free ^{131}I$^-$, and 10 μl (100 μg) of chloramine T. Micropipette is emptied into small tube; 35 seconds later, contents of micropipette *B* are added to neutralize chloramine T. *B* contains 10 μl ($^-$150 μg) of sodium thiosulfate.
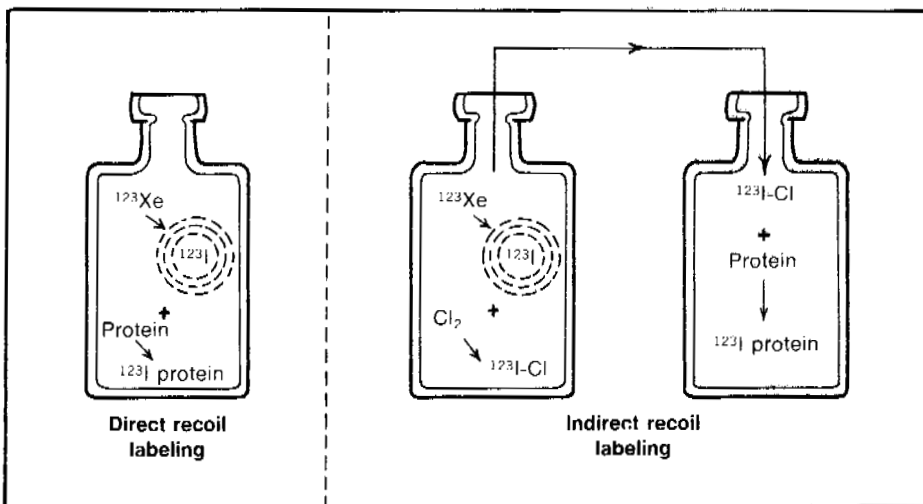
Fig. 10-3. Recoil labeling of proteins in ^{123}Xe/^{123}I generator.

The iodine monochloride (ICl = carrier, *ICl = radioactive form of the molecule) has been used for many years but has now been mostly replaced by newer methods, except when the *ICl is produced by excitation labeling, as just described. This method involves the reaction of *ICl under mild conditions. Presumably, *ICl disassociates into *I' and Cl⁻. The positive iodine atom undergoes replacement reactions. The ICl itself may add across a carbon double bond, followed by the replacement of the chlorine with an iodine stirrer from a second molecule of ICl.

Other methods involve the use of **electrolysis** to make a high-specific activity product under mild conditions and the use of chlorine gas or hypochlorite in solution to oxidize the iodide ion to make it reactive (Fig. 10-4). Both of these approaches have been used to produce excellent products. When direct iodination is impossible, it is sometimes feasible to synthesize a derivative of the parent compound that can be iodinated.

Much of the iodination occurring today is used to label antigens for radioimmunoassay. To be useful, the labeled antigens must retain their antigenic function so that the labeled species will participate in the chemical reactions required for effective radioimmunoassay procedures. Reagents of high specific activity make possible the great sensitivity of this method.

Technetium chemistry

Of all radiopharmaceuticals administered in the United States, 82% to 86% are made with ^{99m}Tc. More than two thirds of these administrations require chemical modification of the technetium as a major step in their formulation. Therefore, this section will explore some of the reactions of technetium in dilute aqueous solution as they are currently understood.

Technetium is element number 43; it is a metal in the second of three rows of the transition elements, which are also called *heavy metals*. It falls between manganese and rhenium and shares many properties with these elements, especially rhenium. Unfortunately, little is known about rhenium chemistry. Although all isotopes of technetium are radioactive, small metallic chunks have been made, and some of its colligative chemical properties have been ascertained.

Our technetium is obtained in solution from the ^{99}Mo/^{99m}Tc generator described in the previous chapter. As such, it is in amounts on the order of 10^{-7} grams in 5 to 30 ml (10^{-9} molar) and is in the chemical form TcO_4^-, which is the oxidation state +7. It is called pertechnetate, analogous to pink permanganate, MnO_4^-, and is the most stable form of Tc in water and air. Pertechnetate is a weaker oxidizing agent than permanganate and a stronger one than perrhenate. The size and charge of pertechnetate are similar to perchlorate, ClO_4^-, and iodide, I^-, so its biodistribution is similar to these ions in that they are all trapped by the thyroid and have similar behavior in the GI and renal systems.

REDUCTION

The radiopharmaceutical chemistry of technetium involves the **reduction** of the pertechnetate ion to one or more of the possible lower oxidation states, between +6 and +3. The charge on the TcO_4^- species is negative, but the charge on some of the ions of these lower states may be positive, permitting positive ion reac-

Protein + KI
+NaCl 0.9%

(−)

Platinum
wire

NaCl 0.9%

(+)

Platinum
vessel

Water
pocket

Magnet
stirrer
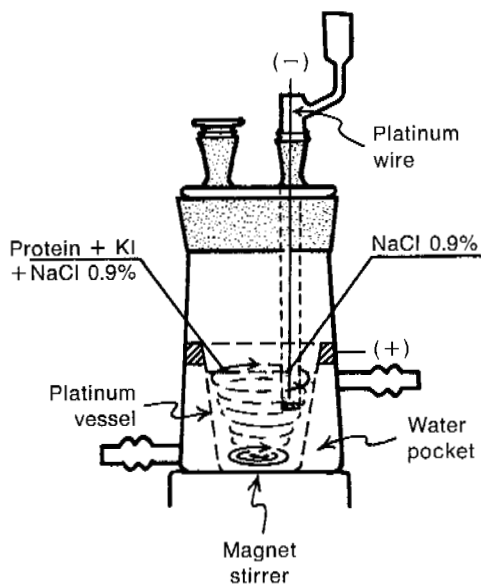
Fig. 10-4. Electrolytic radioiodination. (Modified from Rosa, U.: Atompraxis **6,**1966.)

tions. After reduction of the pertechnetate, the radionuclide can be complexed to a wide variety of compounds chosen to control its biologic behavior. Reduction and complex formation depend on at least the following parameters:

1. **Redox** potentials of Tc state produced and of the reducing agent
2. Concentration of reducing agent, complexing agent, and Tc
3. Complex stability—ability to hold onto the Tc
4. Time after production and temperature
5. Order of adding reagents

The reducing agents employed are, in descending order of utility, Sn^{+2}, Fe^{+2} with ascorbate, $S_2O_3^-$ in acid solution, concentrated HCl, HCl/HI, organic thiols ($-SH$), $NaBH_4$, and electrolysis. Nonmetallic agents do not keep well; the reduction by thiols is complicated by sulfur colloid formation. Electrolysis, with zirconium electrodes, has proved quite successful when it has been used. Stannous ion Sn^{+2}) is the most popular reducing agent, followed by ferrous ion (Fe^{+2}) with ascorbate and thiosulfate ($S_2O_3^-$) in acid solution, which is used for making sulfur colloid.

Let us use the reduction of TcO_4^- by Sn^{+2} as an example of the reduction. Tc(IV) is assumed to be the product. The separate pairs of the redox reaction are:

$$Sn^{+2} \rightleftharpoons Sn^{+4} + 2e^-$$
$$TcO_4^- + 8\ H^+ + 3e^- \rightleftharpoons Tc(IV)^{+4} + 4\ H_2O$$
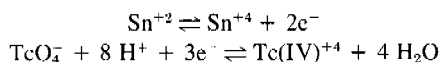
Balancing the numbers of electrons and adding the two reactions together gives

$$2\ TcO_4^- + 16\ H^+ + 3\ Sn^{+2} \rightleftharpoons 2\ Tc(IV)^{+4} +$$
$$3\ Sn^{+4} + 8\ H_2O$$
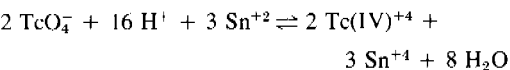
as a balanced redox reaction. Just because this reaction can be written does not prove that it happens. There may be a mixture of Tc(III), Tc(IV), and Tc(V) after reduction, with the proportion of each depending on the conditions. This reaction is reversible and will not keep the Tc reduced to the (IV) state unless it is stabilized by the addition of a complexing agent. Stoichiometrically, it takes only a trace of Sn^{+2} to reduce all the Tc present, but in practice 100 to 400 mg of Sn^{+2} are required to assure an adequate shelf-life for the radiochemical after it has

been prepared. The tin should have no pharmacologic effect when injected; the amounts are far below the levels at which any toxic effects are seen. However, the tin chemically alters red blood cells for several days to make possible the technetium labeling of red blood cells in vivo as well as in vitro. A dose of $^{99m}TcO_4^-$, if it has been injected after a dose of some tin containing a radiopharmaceutical such as a bone scanning agent, will be incorporated into red blood cells. It may be that smaller quantities of tin can be used in the future to minimize this effect.

LIGAND EXCHANGE

Like other heavy metal species, the various Tc ions have unfilled electronic orbitals that can be filled with electrons supplied on other attached chemical groups called **ligands.** Some of the more common ligands are listed here:

> Anions: Cl^-, F^-, OH^-
> Molecules: H_2O, ROH (alcohols), CO
> Groups: Amines, **sulfhydryl,** phosphates

During the reduction process, some or all of the oxygens surrounding the Tc can be replaced by one of the above ligands, depending on its concentration and that of competing ligands in the solution. Ligands can exchange with other ligands (Fig. 10-5); the process depends on the bond strengths and concentration of the competing groups. The kinetics of
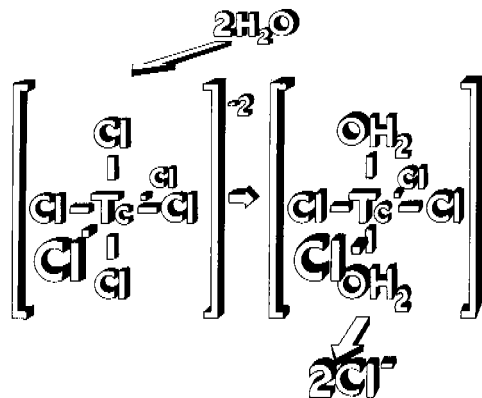
Fig. 10-5. Ligand exchange in which chloride groups surrounding Tc(IV) are displaced by water molecules.

exchange are variable: some exchanges occur instantly; others take several hours. Tc(IV) complexes in which the ligands are OH^- or H_2O can lose water to become the insoluble oxide, TcO_2 (like MnO_2). In neutral or basic solution the reaction is:

$$Tc(OH)_4 \rightarrow TcO_2\downarrow + 2\ H_2O$$
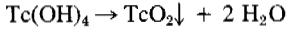
Reduced hydrolyzed Tc(IV) $(H_2O)_n^{+4}$ is capable of oxalation or loss of water between two such complexes in neutral or basic solution.

$$2\ Tc(H_2O)_n^{+4} \rightarrow$$
$$Tc_2O_2 \cdot H_2O_{(2n-4)+4} + 2\ H_2O + H^+$$
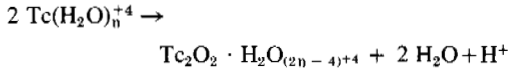
We can speculate that technetium can participate in hybrid **olation** and **oxalation** with metals such as tin, aluminum, or iron in the solution. These reactions could account for the persistence of the reduced hydrolyzed ions in the presence of concentrations of ligands that otherwise would be expected to complex the technetium.

CHELATION

The chelating agents are another class of complexing agents used with reduced technetium. **Chelates** are complexing agents with more than one ligand or complexing site. They are rather like an octopus enfolding the metal ion. The chelates have their own biologic behavior, which the central metal ion does not greatly affect. Two very common chelating agents are EDTA (ethylenediamine tetraacetic acid) and DTPA (diethylenetriamine pentaacetic acid). EDTA is in such common use that its salt has been nicknamed "edetate." Fig. 10-6 shows the chemical structures of EDTA and DTPA.

DTPA has eight possible complexing sites: the three nitrogens and the five carboxylic acids $(-COOH)$. It is unlikely that it can get all its "hooks" onto a Tc(IV) at once. DTPA holds Tc(IV) very tightly, as it does the Pb^{+4} ions; DTPA is used for lead detoxification. It chelates the metal and promotes its excretion by the kidneys. Chelates like DTPA are very efficiently
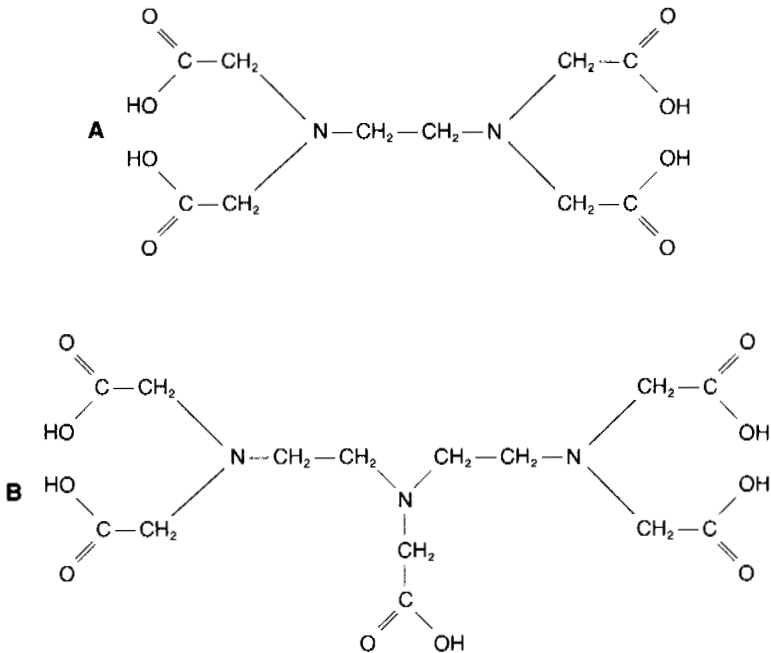
Fig. 10-6. A, Chemical structure of EDTA, ethylenediamine tetraacetic acid. **B,** Chemical structure of DTPA, diethylenetriamine pentaacetic acid.

and quickly transferred from the blood to the urine. This same behavior is observed for Tc DTPA.

Two DTPA preparations are in use today; they illustrate the idea that slight differences in preparation can lead to different products. One

Pyrophosphate   **MDP**

EHDP   **IDP**

Polyphosphate

Fig. 10-7. Phosphate-containing substances that complex reduced technetium to form bone-seeking tracers.

preparation uses Sn^{+2} as a reducing agent and apparently leads to Tc(V) DTPA, Tc(IV) DTPA, and Tc(III) DTPA. If the TcO_4^- is added to an excess of the Sn^{+2}-DTPA mixture, a 50-50 mix of Tc(III) DTPA and Tc(IV) DTPA results. If Sn^{+2} is added to a mixture of TcO_4^- and DTPA, only Tc(V) DTPA results. These materials are excreted rapidly through the kidneys with little retention. The other preparation uses Fe^{+2} ascorbate as a reducing agent and leads to a chelate that appears to hang up in the kidneys and therefore has a lower renal excretion. In this form of the complex, some of the reduced technetium is probably available for ligand exchange onto sulfhydryl groups attached to structures within the kidneys. Thus, as the chelate passes through the kidneys, some of the radioactive tracers become fixed to renal tissues.

Other chelating agents that create soluble compounds are the phosphates and phosphonates, which are shown in Fig. 10-7. These are bone scanning agents. Once reduced, the Tc(IV) can complex with one or more $-PO_3H_2$ groups, depending on the conditions of the reaction. It may be that small differences in the conditions change the relative amounts of the different possible complexes. This may explain some of the variation in biodistribution observed with these tracers.

Another molecule which contains phosphate groups that can complex reduced technetium is

Fig. 10-8. Chemical structure of phytate.

phytate. The molecular structure is given in Fig. 10-8. The Tc phytate complex is formed using the stannous reduction method. The complex is soluble in aqueous solution, but it is immediately precipitated when injected into the bloodstream. Serum calcium precipitates the radiolabeled complex. It is then cleared from the blood by the RE system.

PROTEIN LABELING

Proteins are so designed that they are very effective in complexing or chelating metal ions. A protein molecule has many ligands, so the possibilities for binding technetium are great. Some of the bonds are likely to be less stable than others; thus a fraction of Tc-labeled protein is almost always less stable than the analogous radioiodinated species. Serum albumin is the most readily available human protein. It can be labeled with reduced technetium under a variety of conditions. Initially, the iron–ascorbic acid method was most widely used, but this method always required a separation of the labeled product from residual pertechnetate. The electrolytic method was introduced. It gave higher yields, and thus the final separation could be avoided; however, the reaction conditions were somewhat difficult to control, making product reproducibility a problem. Currently, the stannous reduction method has been perfected so that it works fairly well for protein labeling. The insoluble forms of albumin, macroaggregates, microaggregates, and microspheres are more readily labeled using the tin method than is the native protein. With these forms, the avoidance of reaction conditions that might denature the protein becomes unnecessary, since the proteins are, for the most part, denatured already.

In addition to serum albumin and its derivatives, several other proteins have been labeled with reduced technetium. Included in this group are the proteins involved in thrombogenesis and thrombolysis. In these reactions great care to control the reaction conditions is required because the biologic activities of the molecules must be preserved for the product to be useful as a tracer.

It has also been demonstrated that chelating functional groups can be coupled to proteins and other molecules to provide a means for the stable incorporation of tracer technetium.

SULFUR-BASED REDUCTION PRODUCTS

Sulfur-containing compounds, thiols in particular, are often able to both reduce and complex technetium. Fig. 10-9 gives the structure of several molecules that are used for this purpose. When an acid solution of thiosulfate is heated in the presence of pertechnetate, several reactions occur, including the formation of colloidal sulfur. The technetium is converted from a soluble pertechnetate into an insoluble sulfide. Whether or not the technetium is reduced during the reaction is not established.

When the thioamino acid, penicillamine (Fig. 10-9), is reacted with pertechnetate under basic conditions, a technetium complex is formed that is primarily excreted through the kidneys. Up to 30% of the injected dose ac-

$$HOOC-CH-CH_2-COOH$$
$$|$$
$$SH$$

TMA

$$HOOC-CH-CH-COOH$$
$$|\quad\,\,|$$
$$SH\quad SH$$

DMSA

$$CH_2-CH_2-CH-|CH_2|_4-COOH$$
$$|\qquad\qquad\,|$$
$$SH\qquad\quad\,\,SH$$

DHTA

$$\qquad\qquad CH_3$$
$$\qquad\qquad |$$
$$CH_3-C-CH_2-COOH$$
$$\qquad\quad|$$
$$\qquad\quad SH$$

Pen
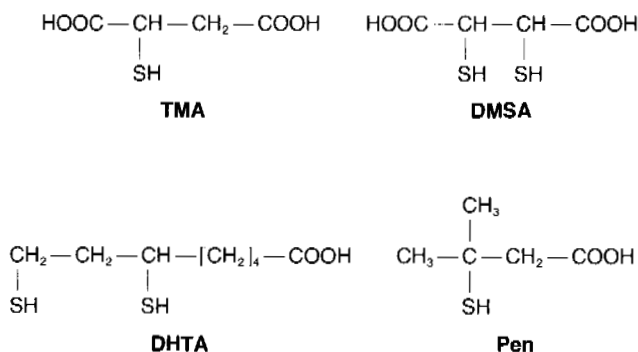
Fig. 10-9. Chemical structure of thiocompounds that both reduce and complex technetium. *TMA*, thiomalic acid; *DMSA*, dimercaptosuccinic acid; *DHTA*, dihydrothioctic acid; *Pen*, penicillamine.

tually becomes fixed in the renal tissues, which makes this complex a good radiopharmaceutical for renal imaging. When this same compound is reacted with pertechnetate in acidic reaction conditions, a different technetium complex is formed that is removed from the blood by the liver rather than the kidneys.

Chelation and complexation of other metals

The discussion of other elements in use in nuclear medicine is by no means exclusive. New compounds and new ways to make and use the old ones are invented every day. The principles will be similar to those already discussed and thus are aimed at drawing together the common threads. We shall begin with the **transition metals** and treat the nonmetals afterward. The compounds made in biologic systems and those relegated to the discipline of organic chemistry will be discussed in other sections.

It can be said about all transition metals that they have multiple oxidation states, one or more of which are stable under air and in water. Because the transition metals have unfilled electronic shells, they can form complexes and chelates of various kinds and strengths. The manipulations of the transition metals for radiopharmaceutical purposes often involve changing the oxidation state. For some of the metals, like technetium, chromium, indium, mercury, and iron, these possibilities have begun to be exploited. For others, such as gallium, cobalt, copper, lead, and arsenic, the chemical manipulations to date have only been of the simplest kind.

Chromium is a transition metal in the first row of the periodic chart. Chromium is an essential trace element. The common oxidation states are Cr(VI), represented by CrO_4^- and $Cr_2O_7^-$, and Cr(III) as Cr^{+3}. Cr(III) is coordinated in water and other solutions, with coordination number of six in an octahedral arrangement. Chelates form even more stable complexes with Cr(III) than do the simple complexing agents. $Cr(H_2O)_6^{+3}$, $Cr(H_2O)_5Cl^{+2}$, and $Cr(H_2O)_4Cl_2^+$ are all known and interchange waters and chlorides in chloride solution. The olation process of splitting out waters be-

tween molecules is documented for Cr(III) where oxygen bridges form square structures of very high stability, as shown in Fig. 10-10. This process can progress to form $Cr(OH)_3$, which is really $Cr(OH)_3 \cdot 3\ H_2O$. In time the chromium precipitates out or forms a colloid. Anions present during the process may be captured. The very strong oxygen bonding may be prevented or even reversed when other competing complexing agents are available. The reverse reaction may be kinetically slow and, therefore, hard to effect. Cr(III) is a label for proteins, apparently as an olated complex. From the chemistry of tanning, the pragmatic use of Cr(III) for protein labeling was developed.

^{51}Cr (323 kev, $T_{\frac{1}{2}} = 27.8$ days) decays by electron capture. It has been used as a label for blood elements. The most common of these is the red cell label. To label red cells, $Na_2^{51}CrO_4$ is mixed with whole blood in a special ACD* solution in vitro. The reaction of the Cr(VI) with the red cells appears to involve reduction and tagging of the ^{51}Cr to the red cells. The reaction is stopped by adding ascorbic acid to reduce and complex unreacted Cr(VI) before the cells are reinjected. Cr(III) is a label for plasma, both in vivo and in vitro. If other blood elements are separated, they can be labeled by reduction of $^{51}CrO_4^-$. The binding is more or less stable, depending on the compound. ^{51}Cr is also a label for albumin, to be used in such GI studies as protein-losing enteropathy diagnosis. Because chromium is not an important body metal, it is not reused by the body for any process. Once the chromium is released in the body from its parent substance, it is excreted from the circulation into the urine and from the GI tract into the feces.

Indium is a metallic element of Group 3. The most stable oxidation state is +3. The ions are complexed to other species in water solution and can form numerous stable chelates. It may be worth noting that gallium and indium have

---

*ACD is acid citrate dextrose, 8 mg citric acid, U.S.P. (anhydrous base), 25 mg sodium citrate U.S.P. (dihydrates), and 12 mg dextrose U.S.P. (anhydrous) qs to 10 ml with water for injection U.S.P. Available from Mallinckrodt, Inc., St. Louis, Mo. 63134, as A-C-D Solution (Modified).
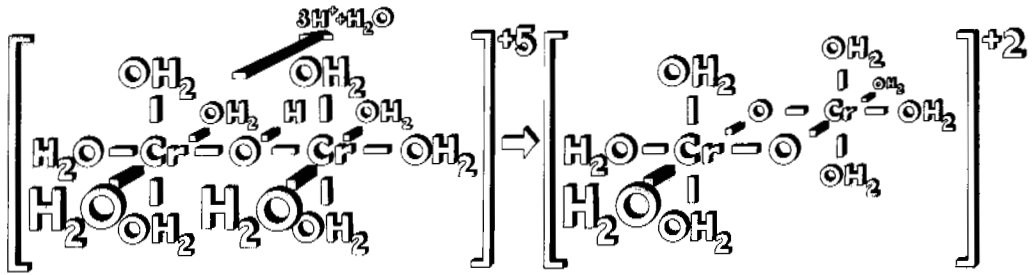
Fig. 10-10. Olation reaction of chromium complex.

many similar chemical properties. The two isotopes of indium are indium 113m (390 kev, 1.7 hours) and indium 111 (173, 247 kev, 67 hours). In DTPA chelates of both isotopes have been used. ^{111}In DTPA is currently the agent of choice for cisternography. The blood clearance half-time of In DTPA is about 70 minutes. It can be used as a brain scanning agent, especially in places where ^{113m}In is more readily available than ^{99m}Tc.

Indium can be labeled to iron hydroxide particles for lung scanning; kits are available outside the United States for such labeling. Liver, spleen, and bone marrow scanning may be performed with an indium colloid made by precipitation of indium at pH 7 to 8 in the presence of a gelatin stabilizer. With indium tracers no radioactivity appears in the gastrointestinal tract or bladder as often happens with technetium-labeled tracers. Indium can be used for blood-pool scanning by injecting gelatin-stabilized InCl$_3$ at pH 3.5 to 4. The indium is bound by transferrin when it is injected into the bloodstream.

Organic and biochemical synthesis

Organic chemistry broadly covers all reactions of carbon. From this chemistry we can find many ways to incorporate radioactive species into carbon-containing compounds. Carbon has the almost unique ability to bond tetrahedrally to itself to form long chains, rings, and complex structures, thus enabling the complex mechanisms that we associate with living systems. Biochemistry or the biologic part of organic chemistry also provides us with many mechanisms for the synthesis of radiolabeled molecules.
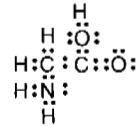
Fig. 10-11. Electronic structure of amino acid, glycine.

The carbon-carbon bond is a covalent bond in which the electrons are shared between the atoms. Carbon-carbon bonds can involve 2 electrons shared between 2, 4, or occasionally 6 carbon atoms, forming single, double, and triple bonds. There are 4 single bonds possible from each carbon atom, 1 single bond from each hydrogen, 2 from each oxygen, and 3 from each nitrogen. The structure of glycine (Fig. 10-11), the simplest amino acid, illustrates these bonding ideas.

Organic synthetic methods are necessary when we wish to incorporate ^{11}C, ^{13}N, or ^{15}O into organic compounds. These must be very rapid because the half-lives of these nuclides are so short. Thus, a subbranch of organic chemistry dealing with fast synthesis has been developed. Very often a metallic surface is used as a catalyst to promote a reaction. The catalyst itself is not changed in the reaction. Alternatively, enzymes may be employed as the catalyst; solid-state enzymes are being developed especially for this purpose. Solid-state enzymes are produced by covalently bonding the enzymatically active proteins to beads or surfaces.

The synthesis of ^{11}C chlorpromazine can be used as an example of organic synthesis. The ^{11}C from the cyclotron production is made into ^{11}CO$_2$ by flowing the cyclotron products across

$^{14}_{7}$N [p,d] $^{11}_{6}$C $\xrightarrow[\Delta \quad CuO]{O_2}$ $^{11}CO_2$

$\downarrow (LiAlH_4)$

H^{11}CHO $\xleftarrow[\Delta]{Ag}$ $^{11}CH_3OH$

+

(phenothiazine structure with S, N, Cl, H, [CH$_2$]$_3$—N, CH$_3$) $\xrightarrow{HCOOH}$ (phenothiazine structure with S, N, Cl, $^{11}CH_3$, [CH$_2$]$_3$ N, CH$_3$)
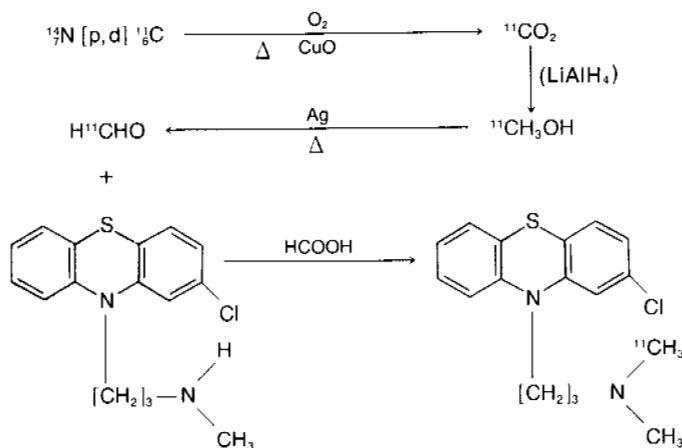
Fig. 10-12. Outline of synthesis of ^{11}C-labeled chlorpromazine.

hot copper with an excess of oxygen. The CO_2 is made into methyl alcohol by reaction of the CO_2 with lithium aluminum hydride and di-ethyl and dibutyl carbinols. The products of the first reaction are carried by flowing nitrogen through silver wool in a furnace, which re-duces the alcohol to formaldehyde. The formal-dehyde then flows to a flask containing nor-chlorpromazine in dimethylformamide and for-mic acid, which functions as a cold trap for the formaldehyde ^{11}C. Once it is trapped, the mix-ture is sealed and heated. Under these condi-tions, a hydrogen atom is replaced by the $-^{11}CH_3$ of the formaldehyde ^{11}C. The product can be extracted from the reaction mixture with ether or separated by gas chromatography. It is made up in saline and purified through a Milli-pore filter. From the time the $^{11}CO_2$ is made, the synthesis takes 25 minutes if the ether ex-traction method is used. About 7% of the radio-activity is in the product. Thus, the amount of activity to start with must be about a hundred times that needed at the end. The reaction se-quence is outlined in Fig. 10-12.

Biochemical synthesis involves the use of en-zymes as catalysts to promote the reaction. The enzymes are large organic molecules synthe-sized by living systems that have certain active shapes to their electron shells. Apparently, the enzymes act as templates. The reactants sit down on the template and are thus arranged into an electronic configuration that facilitates the reaction and causes it to be very specific. The enzymes have very complex chemical structures: even if we could write them down, we would not want to do it very often because they would be so large *and* their spatial char-acteristics would not be obvious from a two-dimensional picture. Thus, the enzymes are named for what they do, not for their struc-ture. A dehydrogenase, for instance, catalyzes the removal of $-H$ from a particular site in a particular compound. The *-ase* ending indicates that the substance is an enzyme.

The synthesis of ^{13}N-*l*-alanine can be used to illustrate the enzymatic methods. $^{13}NH_3$ is ob-tained from the cyclotron and is trapped in acid. It is separated from the acid by ion-exchange chromatography under pressure. At this point, 80% to 90% of the initial radioactivity is pres-ent in an NaOH solution of pH 8.2. The ammo-nia solution is incubated with an enzyme, glu-tamic acid dehydrogenase, and a salt of glu-tamic acid while pyruvic acid is incubated with glutamic-pyruvic transaminase. The two solu-tions are mixed, and both ^{13}N-*l*-alanine and ^{13}N-*l*-glutamic acid result. The sequence of re-actions is shown in Fig. 10-13.

Biologic synthesis

When the synthetic systems of chemistry and biochemistry do not produce a product with the requisite ease, speed, or specificity, a biologic system may be called into service. Vitamin B_{12},

$$^{12}_{6}CH_4 - [d,n] - ^{13}_{7}NH_3$$

$$+$$

$$HOOC - CH_2 - CH_2 - C \cdots COOH$$
$$\parallel$$
$$O$$

Glutamic
acid
dehydrogenase
→
NADH

$$CH_3 \cdots CH \cdots COOH$$
$$\vert$$
$$^{13}NH_2$$

$$+$$

$$HOOC - CH_2 - CH_2 - CH - COOH$$
$$\vert$$
$$^{13}NH_2$$
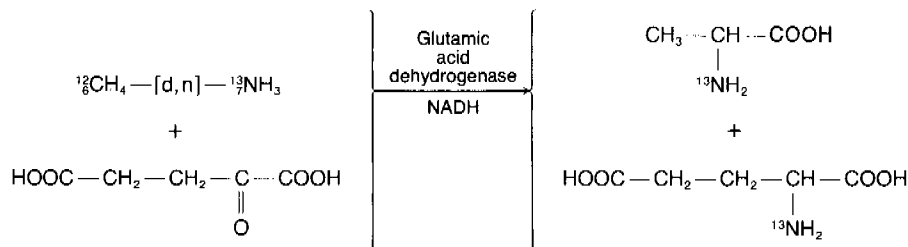
Fig. 10-13. Outline of synthesis of ^{13}N-labeled *l*-alanine and *l*-glutamic acid.

Table 10-1. Properties of radioactive cobalt isotopes

Isotope	Half-life	Principal gamma rays
^{57}Co	270 days	120 kev
^{58}Co	72 days	35 kev
^{60}Co	5.2 years	1.17, 1.33 mev

which contains cobalt at the heart of the molecule, is made commercially by bacterial synthesis. A bacterium, such as *Streptomyces griseus*, is harvested after it has multiplied through many generations. If radioactive cobalt is added to the growth medium, radioactive vitamin B_{12} will result. ^{57}Co, ^{58}Co, and ^{60}Co have been used as labels. Table 10-1 compares the radioactive properties of these isotopes. The labeled vitamin B_{12}, in submicrocurie amounts, is used to study vitamin B_{12} metabolism and **kinetics.** The long biologic half-life of vitamin B_{12} requires a tracer with a long physical half-life in order to trace the substance completely.

One element may profitably be substituted for another under certain circumstances. We see this occurring in the chemistry of certain species, such as $SO_4^=$ and $S_2O_3^=$, where a sulfur substitutes for an oxygen. The human body is satisfied under some but not all circumstances when a substitution is made that involves elements with similar electronic and chemical properties. One of these substitutions, which has not been used nearly so much as it could be, is the substitution of Se for S. Selenium falls under oxygen and sulfur in the periodic chart. It can be substituted for sulfur in the sulfur-bearing amino acids, cys-

tine and methionine. The most common radiopharmaceutical use of selenium is as ^{75}Se in ^{75}Se selenomethionine. It participates in protein synthesis where methionine does and can thus be used to image the pancreas and the parathyroid glands and for many metabolic studies. It can be prepared by chemical synthesis or by growing yeast in a low-sulfur, high-^{75}Se medium. It is possible to make selenium-labeled antibodies in vivo in animals. ^{75}SeO$_3^-$ can be metabolized to ^{75}Se(CH$_3$)$_2$ in the liver; the ^{75}Se(CH$_3$)$_2$ measured in the breath is an indicator of liver transmethylation function.

^{11}C glucose is made photosynthetically by Swiss chard. The Swiss chard is grown and then put in the dark. After the ^{11}CO$_2$ is prepared, it is put into the atmosphere around the Swiss chard, and the lights are turned on. The Swiss chard uses the ^{11}CO$_2$ to make glucose. After a few minutes of exposure, the Swiss chard is ground up and the glucose extracted.

White blood cells can be labeled in vitro using a biologic method. The cells are separated by centrifugation from the other blood components. They are then mixed with ^{99m}Tc-labeled albumin minimicrospheres less than 3 μ in diameter. The cells ingest the microspheres and are then reinjected. Labeled white cells can be used to image abscesses.

The human body is also used at times as a biosynthetic system. Inorganic iron, ^{59}Fe, is incorporated into red blood cells; ^{131}I$^-$ is incorporated into thyroid hormone. ^{75}Se can be used in vivo as a label in many systems in place of sulfur. The analogy between Se and S can be established by the comparative testing of ^{75}Se compounds against their ^{35}S analogs in animals.

Suggested readings

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Daily preparations and their quality control

At the present time almost all radiopharmaceuticals compounded in radiopharmacies are ^{99m}Tc compounds. These compounds have half-lives of 6 hours and shelf-lives of from ½ to 24 hours, which means that the preparations must be made daily.

Routine quality control
GENERAL REQUIREMENTS

When an NDA*-approved kit and an NDA ^{99m}Tc generator are used and the person preparing the radiopharmaceutical follows the instructions exactly for both the generator and for the kit, there is no legal demand that quality control tests be performed. The generator has been designed, as have the kits, to ensure a very high probability of success in the preparation of the radiopharmaceuticals when the instructions are followed. Quality control tests serve as an internal check to assure that the person preparing the radiopharmaceutical has not made some blunder in carrying out the instructions. In a few cases, the kits themselves have not been 100% reliable, so quality control also permits the preparer to assure that the kit used gives satisfactory tagging. Quality control tests can also provide information about whether the preparation was successful in situations in which following the exact instructions was not feasible or was not what the preparer deemed best for the current situation. For instance, if the kit instructions state that the maximum number of millicuries to be added in the preparation is 30 mCi and if the kit was prepared us-

ing 40 mCi, then the person who modified the manufacturer's instructions is obliged to establish the quality of the product and to demonstrate that the modification did not cause substandard performance.

THIN-LAYER CHROMATOGRAPHY

Thin-layer chromatography (TLC) is the most widely used method for rapid determination of radiochemical impurities in radiopharmaceuticals. Many commercially available systems are satisfactory for the performance of these tests (Fig. 11-1); however, an easy-to-use system may be designed in-house that is much less expensive than the commercial products. Levit, Adams, and Rhodes* explain the construction and use of one such system.

In general, a microdrop of the radiopharmaceutical is spotted on a dry-gel that is fixed to a support matrix such as fiberglass. This TLC gel is often a small strip that can be placed in a small jar containing less than a milliliter of the **solvent.** The solvent migrates up the gel and moves away from the origin any materials that are solubilized. The insoluble forms of the tracer remain where they were spotted. Development usually requires 3 to 5 minutes. When the solvent has reached the top of the strip, it is removed and allowed to dry. Usually, it is sufficient to merely cut the strip into two parts, the origin (or bottom one third to one half of the strip) and the solvent front (or upper one half to two thirds of the strip). After counting both pieces and subtracting background, the percent

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*New Drug Application approved by the Food and Drug Administration.

*Levit, N., Adams, R., and Rhodes, B. A.: Manual of radiopharmacy procedures, Cleveland, CRC Press, Inc. (in press).
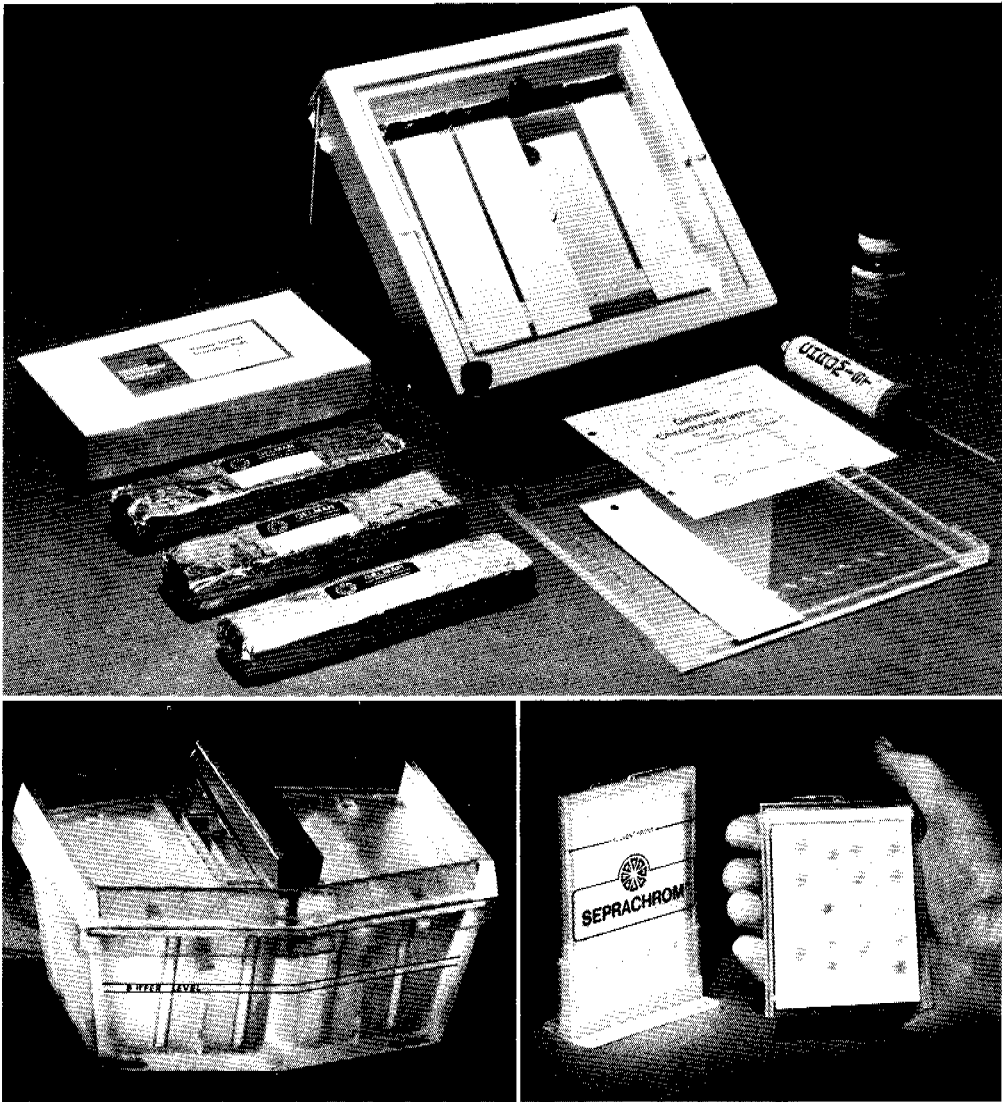
Fig. 11-1. Commercially available kit and reagents for doing thin-layer chromatography.

soluble or insoluble radioactivity is calculated. When acetone is used as the developing solvent, technetium complexes, particles, and oxides are insoluble; only free pertechnetate is soluble. Acetone is used when we assay for free pertechnetate. When saline is used as the solvent, technetium complexes and free pertechnetate are soluble; hydrolyzed technetium and technetium particles remain at the origin. Saline is used when we assay for hydrolyzed technetium in complexes such as ^{99m}Tc DTPA,

^{99m}Tc-labeled proteins, or ^{99m}Tc-labeled bone agents.

GEL-COLUMN SCANNING

The radiochemical purity of routinely prepared ^{99m}Tc products can also be determined by gel-column chromatography (Fig. 11-2). A drop of the radiopharmaceutical is placed on the column; after the drop enters the gel bed, a volume of solvent equal to the void volume of the column is added. Once the solvent has passed
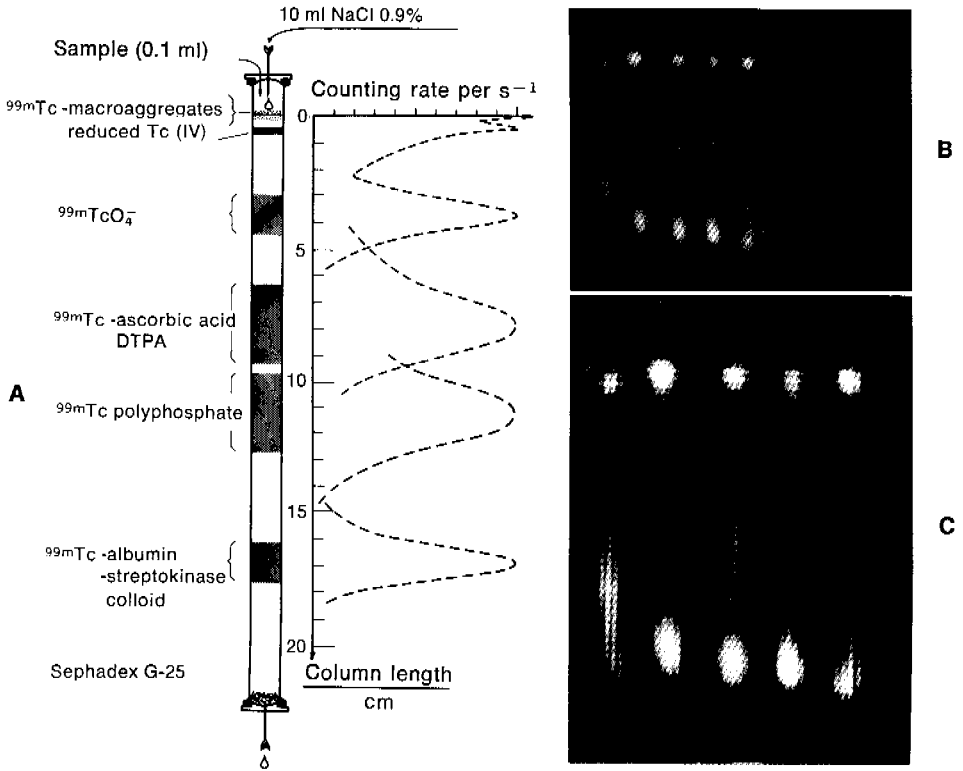
Fig. 11-2. Gel-column chromatography. **A,** Distribution of different ^{99m}Tc compounds on columns. **B** and **C,** Gamma-camera images of columns. (From Persson, B. R. R.: Gel chromatography column scanning. In Rhodes, B. A.: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.)

through the column, the different ^{99m}Tc species will have moved various distances down the column. The columns are scanned or imaged to determine the relative amounts of the different ^{99m}Tc chemical species.

Sodium pertechnetate solution

The two primary sources of sodium pertechnetate solution are (1) instant ^{99m}Tc solution, which is purchased on a daily basis and is ready to use as is, and (2) ^{99}Mo/^{99m}Tc generators, which the user elutes with sterile saline as ^{99m}TcO$_4^-$ is needed. Generators are eluted by following the instructions supplied by the manufacturer. In principle this involves passing a sterile solution of 0.9% sodium chloride through the alumina column that contains the ^{99}Mo; the ^{99m}Tc formed by the molybdenum decay is soluble in the saline, whereas the

molybdenum itself is not. Thus, as the saline passes through the column, 75% to 85% of the ^{99m}Tc contents of the column is washed out with the saline. The saline with the ^{99m}Tc is usually collected in an evacuated, sterile, pyrogen-free vial. Aseptic techniques are used in the elution of the generator to prevent contamination of the generator and of the eluate with microorganisms, pyrogens, or foreign particles.

The generator column is housed in a lead shield to protect the operator from radiation. The operator should always place the elution vial in a lead container to minimize the radiation exposure during the elution process. Elution of generators usually takes 3 to 10 minutes. During the waiting time, the operator should step away from the generator to avoid unnecessary radiation exposure. When the elution is completed, the vial in the lead container

Fig. 11-3. Radiation dose calibrator. (Courtesy Capintec, Inc.)

is removed, and the ^{99m}Tc content is assayed. The operator next faces the problem of determining the concentration of the radioactivity in the eluate and its radionuclidic purity. In some laboratories, the radiochemical purity of the pertechnetate is also determined, using thin-layer chromatography.

ELUTION VOLUME

The method that has been used most frequently for the determination of the volume of the eluate is visual inspection after removing the vial from the shield with tongs. Working behind a leaded glass shield, the radiopharmacist visually examines the vial, which has calibration markings in milliliters. Visually determining the volume is easy, but it is not very pre-cise, and it exposes the operator to some radiation. Usually, however, operators become very fast and can carry out the procedure with minimal radiation exposure. An alternate way is to use a scale. The empty vial in its lead shield is weighted and recorded as the tare weight. After the elution, the vial is reweighed in the same shield. The difference is the volume of the solution eluated from the generator. This method takes a little longer but has the advantages of being precise and eliminating radiation exposure.

ASSAY OF TOTAL RADIOACTIVITY

One way to measure the total activity in the vial is to transfer the vial with tongs from its shield into a dose calibrator (Fig. 11-3). The

radiation level is directly read from the dose calibrator. In order to get precise measurement by this method, the dose calibrator must have been calibrated with a standard calibration check source traceable to an NBS standard. Also, the dose calibrator must have a linear response. By this, we mean that the readout is proportional to the radioactivity being measured in the range from a few microcuries up to the total activity of the eluate (usually 1 to 2 curies). Also, for precision the operator needs to know the correction factors for the elution vial and for the volume of eluate contained in the vial. For many of the modern dose calibrators this correction factor is very close to 1.

Another method for determining the radioactivity of the eluate is to remove, using aseptic techniques and working behind a leaded glass shield, exactly 1 ml of the eluate. This 1 ml is assayed in the dose calibrator, which has the advantage that the operator does not have to transfer and expose himself to the entire source of ^{99m}Tc irradiation. The value directly measured is concentration. This method is especially useful when the total amount of ^{99m}Tc is outside the linear range of the dose calibrator. The disadvantage of the method is that manual manipulations of the radioactivity are required, and the determination of the concentration is subject to several errors. One error is the dead space in the syringe; that is, the measurement of an exact 1 ml volume with a syringe is usually not precise because some volume of solution is contained in the needle and in the hub of the syringe onto which the needle is fastened. This dead space varies with different syringes. This error can be overcome by weighing the syringe to determine its exact volume. A second loss of precision is that the measurement of the radioactivity in syringes may not necessarily be precise because the position of the syringe in the calibrator is difficult to reproduce exactly. Again, a correction factor may be used. Usually the errors of measurement are insignificant in the handling of technetium 99m solution.

ASSAY OF RADIONUCLIDIC PURITY

Specially designed vial containers are available for holding the technetium solutions in the elution vials that effectively shield out the ^{99m}Tc gamma rays (140 kev) but permit the passage of the more energetic ^{99}Mo gamma rays (740, 780 kev) (Fig. 11-4). The ^{99}Mo in a vial and housed in one of these shields can be counted using gamma-ray spectrometry. The spectrometer is set to accept pulses between 600 and 900 kev. The shielded solution is counted, and the gamma-ray emission in the 600 to 900 range determined. Subsequent to this, the ^{99m}Tc solution is replaced with a ^{137}Cs source. This is counted under identical conditions. The ^{137}Cs sources available for this purpose are calibrated in terms of equivalent microcuries of ^{99}Mo. The amount of ^{99}Mo in the solution is calculated using ratios of cpm/mCi. Alternatively, some dose calibrators are equipped for the measurement of the ^{99}Mo content directly. Again, a special shield must be used; this is supplied by the manufacturer of the calibrator. The ^{99m}Tc solution in the special shield is inserted into the calibrator and the instrument set for ^{99}Mo. The microcuries of ^{99}Mo in the ^{99m}Tc solution are read directly.
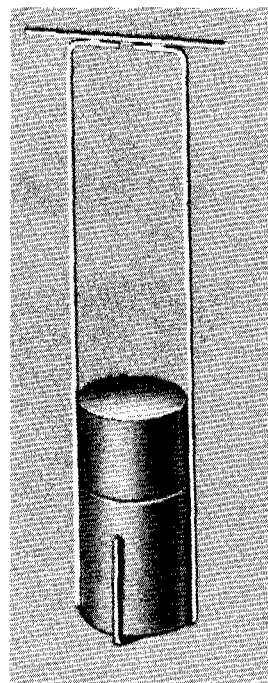
Fig. 11-4. Shield for assay of ^{99}Mo in ^{99m}Tc solution. (Courtesy Capintec, Inc.)

There have been times when ^{99m}Tc solutions have been contaminated with iodine 132 ($T_{\frac{1}{2}}$ = 2.3 hours; 670, 770 kev). This is revealed by gamma-ray spectrometry of the shielded eluate or by the fact that the determination of the ^{99}Mo breakthrough is high, but when it is reassayed an hour or so later, the ^{99}Mo breakthrough has apparently significantly decreased. This means that the gamma rays from the ^{132}I were being assayed as ^{99}Mo radioactivity. Because of the short half-life of the ^{132}I, the repeat assay gives a different and lower value.

Multichannel gamma-ray spectrometry is also used to determine radionuclidic purity (Fig. 11-5).

ASSAY OF RADIOCHEMICAL PURITY

Using a syringe with a very fine needle, a small amount of the solution is removed from the vial into the needle. Then, this drop of a few lambda in volume is transferred to a small strip of TLC medium, which is developed with 85% methanol. The percentage of the radioactivity with an $R_f = 0.68$ (TcO_4^-) is determined. Usually, it is easiest to determine the percentage of the radioactivity remaining at the origin and subtract this from the remainder of the radio-

activity on the strip. This gives the percent of ^{99m}Tc pertechnetate in the ^{99m}Tc solution.

SPECIFIC ACTIVITY

^{99m}Tc decays to the long-lived isotope ^{99}Tc. The concentration of technetium in solution (i.e., ^{99}Tc + ^{99m}Tc) remains constant. During chemical manipulations, the ^{99}Tc competes stoichiometrically with the ^{99m}Tc in oxidation-reduction reactions and in tagging reactions. The amount of ^{99}Tc depends on the previous history of the solution. Total technetium accumulation depends on the millicuries of molybdenum in the generator and the time elapsed since the last elution. If a generator has been sitting for several days without elution, it will contain more total technetium atoms than a generator that has been eluted the previous day. The reader is referred to Lamson, Hotte, and Ice* for the radiation-decay equations that allow for the calculation of the technetium content in pertechnetate solutions.

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*Lamson, M., III, Hotte, C. E., and Ice, R. D.: Practical generator kinetics, Nucl. Med. Tech. **4:**21-27, 1976. (See Appendix B for a revised version of the original article.)
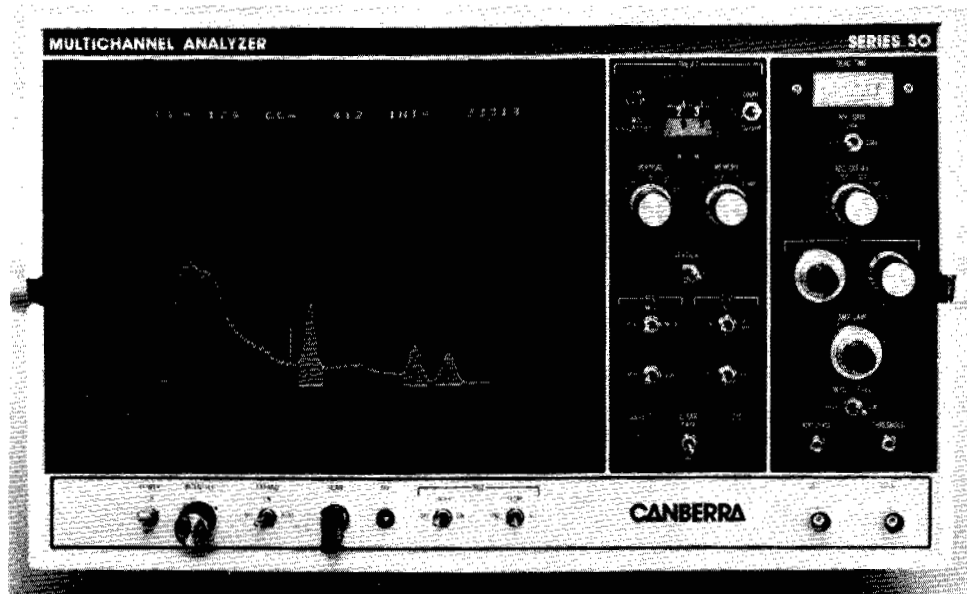
Fig. 11-5. Multichannel analyzer attached to NaI(Tl) crystal detector, used for determination of radionuclidic purity. (Courtesy Canberra Industries, Meriden, Conn.)

ALUMINUM BREAKTHROUGH

In the past, some generator columns released Al^{+3} ions into the ^{99m}Tc eluates. These ions can interfere with tagging reactions. Tests for aluminum breakthrough have been developed to check for this problem. Spot test procedures are commercially available. Some generator manufacturers supply the spot test reagents with their generators. *The United States Pharmacopeia* provides a standardized method for measuring aluminum breakthrough in pertechnetate solution. With current generator systems, aluminum breakthrough is rarely a problem.

LABELING AND RECORD KEEPING

Each time a generator is eluted, the results of elution are recorded (Fig. 11-6). Data usually include elution number, time of elution, millicuries of ^{99m}Tc obtained, volume of the eluate, ^{99}Mo breakthrough, and routine quality control test results. The vial containing the Tc is labeled both with total millicuries contained, concentration in millicuries per milliliters, and time of calibration. The Tc solution in its shield is put in a lead storage well for further use. If there is a significant amount of ^{99}Mo breakthrough, the operator must also calculate the expiration time of the pertechnetate solution (the time when the concentration of ^{99}Mo, with respect to the ^{99m}Tc, will exceed 1 μCi/millicurie), as well as the maximum volume that can be administered to a patient; this volume is the number of milliliters that contain 5 μCi of ^{99}Mo.

^{99m}Tc colloids

^{99m}Tc sulfur colloid (^{99m}Tc SC) is the most widely used liver- and RES-scanning radiopharmaceutical. Several sources of NDA kits are available for the preparation of the colloid. In principle, the chemistry of these kits is the same. $^{99m}TcO_4^-$ is added to a solution of thiosulfate (Fig. 11-7). Acid, HCl, is added, and the vial heated in boiling water. In hot acid solution, thiosulfate reacts to form colloidal sulfur. After heating for a few minutes (see instructions supplied by the manufacturer, but it is usually about 10 minutes), the colloidal suspension is cooled, and a **buffer** is added to neutralize the excess acid. Stabilizers are contained in one or the other of the solutions. Gelatin, a heat-stable protein, is often used. Proteins coat colloids and inhibit particle size growth.

Fig. 11-6. Sample of laboratory control sheet used to record results of each elution of ^{99m}Tc generator.
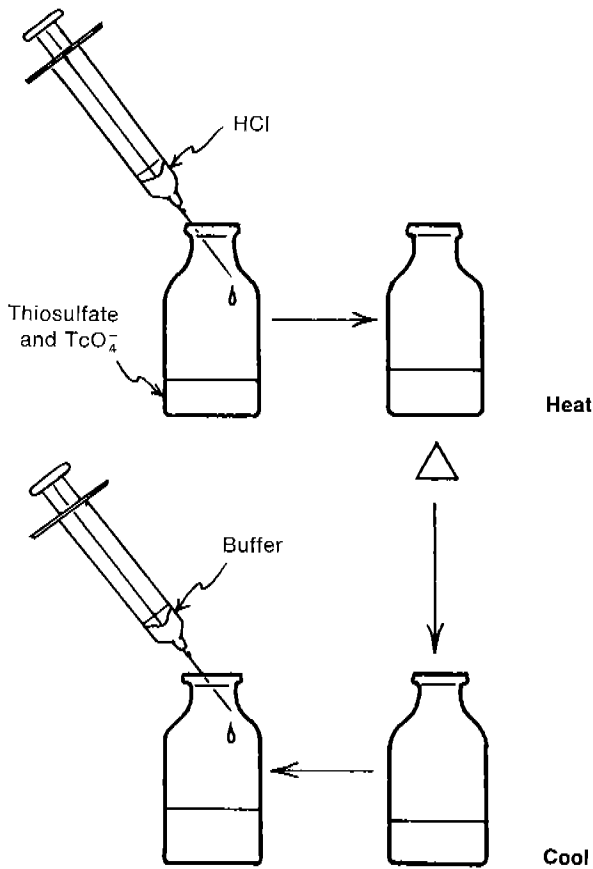
Fig. 11-7. Scheme for preparation of ^{99m}Tc sulfur colloid.

During the reaction, the technetium becomes fixed to the colloidal sulfur, perhaps as insoluble Tc_2S_7 (technetium heptasulfide) or as a reduced Tc species such as TcS_2. The chemical identity of the technetium in ^{99m}Tc SC has not been established. However, subsequent oxidizing conditions can cause release of free ^{99m}TcO$_4^-$ in the preparation; from this we infer that the tagged product may involve a reduced species of technetium.

The particle size distribution of a colloid depends on factors such as rate of formation, concentration, rate of cooling, type and concentration of stabilizer, aging, time, concentrations of Al^{+3} and Fe^{+3}, and probably many others. These factors cannot be reproducibly controlled; thus ^{99m}Tc SC's have a great variety of particle sizes. Furthermore, the particle size in a preparation is undergoing constant change. For-

tunately, the RES is not very particular; when healthy, it is highly efficient at removing colloids of almost any size. However, if the particles get too big, they can be trapped in the capillary beds before getting to the liver, spleen, or bone marrow. Thus, when radioactivity is seen in the lungs of the patient having a liver scan, it may be due either to (1) large particles in the preparation or (2) RES activity in the lungs. Quality control of the particle size distribution is necessary to assist the physician in the interpretation of such a finding. The quality control test is to examine the preparation microscopically. A satisfactory preparation will contain no particles large enough to visualize. Since particle size increases as the preparation ages, it is necessary to perform this test at the time of the injection or very soon after the scan has been completed. A definitive answer to

the particle size question can, at times, necessitate an animal biodistribution study.

TLC in 85% methanol, acetone, or saline can be used to determine the presence of free $^{99m}TcO_4^-$ in ^{99m}Tc SC. The colloidal ^{99m}Tc will remain at the origin in any of the previously mentioned solvents while the $^{99m}TcO_4^-$ migrates. The presence of $^{99m}TcO_4^-$ in the radiopharmaceutical will complicate the interpretation of the liver-spleen images because the shadow of the stomach may be seen. If this is suspected, imaging the neck to look for thyroidal uptake of $^{99m}TcO_4^-$ may be useful. Also, a repeat TLC for free $^{99m}TcO_4^-$ is useful. These quality control tests provide additional information that helps the physician in the interpretation of the images. Technologists should be alert to these signs and should feed back data to the radiopharmacy when evidence of radiochemical impurity is seen on the scans.

Colloidal particles tend to stick to surfaces. Thus, some preparations of ^{99m}Tc SC will decrease in concentration of radioactivity much faster than predicted from radioactive decay alone. Sometimes the particles have been found to adhere to syringes or tubing when the dose is administered through an indwelling catheter.

Some clinics employ ^{99m}Tc tin colloid or ^{99m}Tc phytate. Since the phytate does not precipitate as a colloid until it reacts with plasma calcium, the problems of colloidal aging are avoided with this radiopharmaceutical. Quality control of these two agents is the same as that used for ^{99m}Tc SC.

^{99m}Tc lung agents

Lung agents in current use are particles of denatured albumin treated with stannous chloride and solubilizing agents and then freeze dried, frozen, or sealed in glass ampules. Two types of particles are available: microspheres, in which the albumin is spherized by homogenization in oil and solidified by heating, and macroaggregates, in which the albumin is denatured by heat or chemical treatment in an agitated aqueous solution. The albumin is treated with $SnCl_2$ either before or after the particles are formed. When these tin-treated particles are mixed with $^{99m}TcO_4^-$ solution, the technetium is reduced by the stannous ions. The reduced

^{99m}Tc becomes chemically bound to the particles or precipitates within the particle matrix or onto the surface of the particles. Whatever the mechanism, the reduced technetium becomes firmly associated with the particles.

Problems encountered with these preparations are (1) incomplete reduction, (2) reoxidation of the technetium, (3) clumping of the particles, (4) binding of the Tc to something other than the particles, (5) nonuniform labeling of the particles, and (6) too many or too few particles. TLC analysis for free $^{99m}TcO_4^-$ later in the day usually reveals some reoxidation. Clumping is revealed by microscopic studies. Binding of the Tc to something other than the particles is revealed by poor lung uptake of the tracer. Nonuniform labeling is revealed by microautoradiographic studies that cannot be performed quickly; thus, the need for this is usually avoided by carefully following manufacturer instructions regarding agitation during the labeling process. The specific activity in units of millicuries/100,000 particles reveals whether a dose will contain too few or too many particles. If fewer than 40,000 particles are administered, the lung scan may appear inhomogenous because of statistics alone. If more than a million particles are administered, excessive capillary blockage occurs. This probably is not dangerous until several millions of particles are administered. Ideally, one dose contains $150,000 \pm 100,000$ particles.

^{99m}Tc bone agents

Compounds containing two or more phosphate groups frequently form complexes with technetium that has been reduced by stannous ions. Several of these technetium phosphate complexes are routinely used as bone scanning agents. The chemical structure of the complexes formed with technetium have not been elucidated. It is likely that several different complexes may be formed with a single complexing agent and that each of the complexes has a somewhat different in vivo stability and biodistribution. Such a phenomenon may contribute the nonreproducibility of the performance of bone imaging agents. If a preparation is injected too soon after the $^{99m}TcO_4^-$ is added, the more desirable complexes may not

have reached their equilibrium concentrations; if the preparations are injected too long after the $^{99m}TcO_4^-$ is added, reoxidation may have occurred, releasing free $^{99m}TcO_4^-$ back into the preparation. Another problem with the agents is **hydrolysis** of the reduced technetium, forming insoluble ^{99m}Tc that is localized in the RES rather than the bone. Hydrolysis is probably dependent on pH, age, temperature, total technetium ($^{99}Tc + {}^{99m}Tc$), Sn^{+2} and Sn^{+4}, and other trace metal–ion concentrations. Although total tin is fixed by the kit manufacturer, the ratio of Sn^{+2} to Sn^{+4} may vary even between kits from the same lot. Traces of moisture in individual vials left over from the freeze-drying process probably are a major contributor to the problem of variations of quality of preparations made from kits of the same lot.

Radiochemical quality control tests that can predict the in vivo performance of ^{99m}Tc bone agent have yet to be devised. Fortunately, the images are often diagnostic, even when image quality is poor. TLC is used to detect a major preparation failure such as incomplete reduction of the $^{99m}TcO_4^-$ or high levels of initial hydrolysis. Two solvent systems are used: acetone can be used to separate out free $^{99m}TcO_4^-$, and saline is used to separate hydrolyzed ^{99m}Tc (the $^{99m}TcO_2$ remains at the origin while the $^{99m}TcO_4^-$ and the ^{99m}Tc complexes migrate). TLC used later in the day reveals reoxidation or hydrolysis that occurs with aging. An animal biodistribution study (Fig. 11-8) has been developed that probably predicts the in vivo performance in man, but a correlation study has not been reported in the literature. This is the 30-minute femur-to-liver ratio in mice. If the percentage of injected dose in the femurs is greater than that of the liver, then the tracer's in vivo performance is up to par.

The variable performance of ^{99m}Tc bone agents has also been attributed to metabolic, biochemical, and perhaps medication parameters of the patient. In one study, Wiegmann et al.* showed that hydroxyproline levels correlate with image quality.

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*Wiegmann, T., Kush, J., Rosenthall, L., and Kaye, M.: Relationship between bone uptake of ^{99m}Tc-pyrophosphate and hydroxyproline in blood and urine, J. Nucl. Med. **17**:711-718, 1976.

Fig. 11-8. Scintigram of biodistribution of ^{99m}Tc pyrophosphate in rabbit.

^{99m}Tc DTPA

The chemical structure of diethylenetriamine pentaacetic acid was studied in the previous chapter. In the presence of DTPA and stannous ion, $^{99m}TcO_4^-$ is reduced and complexed by the DTPA. The redox state(s) of the Tc and, thus,

the nature of the complexes formed with DTPA may be variable depending on several reaction variables. Since DTPA forms a very stable complex with technetium, the problems of oxidation and hydrolysis are less frequently encountered with this radiopharmaceutical. TLC, however, reveals these same two radiochemical impurities, as we observed in the ^{99m}Tc bone agents. The available TLC tests do not differentiate the different DTPA complexes. A single biodistribution study in mice can be used as a quality control test. If the ^{99m}Tc DTPA complex has the appropriate in vivo behavior, it is not bound to any tissues and is excreted rapidly and quantitatively into the urine. In fact, more than 90% is excreted by the mouse during the first 30 minutes after intravenous injection.

^{99m}Tc DTPA is most widely used for brain imaging studies and for dynamic renal function studies. If the images are contaminated with ^{99m}TcO$_4^-$ in appreciable amounts, their quality is somewhat degraded, and the quantitative analysis of the renal study loses precision.

When ^{99m}TcO$_4^-$ is reduced with iron and ascorbic acid in the presence of DTPA, a renal imaging agent is formed. Other ^{99m}Tc–renal imaging agents include ^{99m}Tc glucoheptonate, ^{99m}Tc DMSA, ^{99m}Tc penicillamine, and the various bone scanning agents.

^{99m}Tc HSA

Human serum albumin (HSA) was originally labeled with ^{99m}Tc by reducing pertechnetate with iron and ascorbic acid. The residual unreacted ^{99m}TcO$_4^-$ was removed by anion exchange. The product was always contaminated with more than 5% free ^{99m}TcO$_4^-$.

Subsequently, more efficient methods have been developed. At least two of these procedures have had INDs filed by commercial companies. Recently, an NDA on ^{99m}Tc HSA was approved. The older of these methods is the electrolytic method. By this procedure an electric current is used to reduce the ^{99m}Tc. After reduction, the product must be aged for up to 30 minutes to permit binding of the ^{99m}Tc to the albumin. There is considerable chance for operator error with this technique, so quality control testing with TLC should always be employed to ensure that tagging has occurred. Also, particle

contamination is common so that either the quality control test for particles (visual inspection) or Millipore filtration to remove particles should be used. The in vivo stability of the product can be determined by animal distribution studies. The percentage of injected dose in the blood of mice should be greater than 40% at 30 minutes.

Albumin can also be labeled by reducing ^{99m}TcO$_4^-$ with Sn^{+2} in the presence of albumin. In the past, most procedures employing this principle yielded a product contaminated with insoluble ^{99m}Tc and a labeled product that cleared from the blood faster than ^{131}I HSA or ^{99m}Tc HSA prepared by other methods. Recently, the technique has been refined so that it has become possible to prepare ^{99m}Tc HSA with a rapid single-step kit and obtain a product of satisfactory quality. The product is relatively unstable. Reoxidation of the technetium results in a buildup of free pertechnetate that limits the shelf-life to about 3 hours.

^{99m}Tc RBCs

In vitro labeling of red blood cells (RBCs) can be achieved with Sn^{+2} as the reducing agent. Several procedures have been perfected. Probably the simplest is the Brookhaven method. Evacuated blood sampling tubes are prepared containing freeze-dried anticoagulants and the reducing agent. The cells are separated by centrifugation, then added to a saline solution containing high–specific activity ^{99m}TcO$_4^-$. The labeling (approximately 97%) occurs during the next 5 minutes. The labeled cells can be heat damaged with a 15-minute incubation at 49° C to prepare cells that will be sequestered by the spleen. Free ^{99m}TcO$_4^-$ can be determined by TLC or by centrifugation and can be removed by centrifugation.

In vivo labeling of RBCs can be achieved by first injecting the patient with stannous pyrophosphate followed by an injection of ^{99m}TcO$_4^-$ solution. One procedure is to dissolve the entire contents of a Mallinckrodt PYP kit* in 5 ml of sterile saline, then immediately administer intravenously the entire 5 ml to the patient.

*This is, at the time of this writing, not an NDA-approved indicated use for this drug.

Within the next 30 minutes the $^{99m}TcO_4^-$ is administered. This provides an excellent cardiac blood pool agent for both nuclear angiography and gated blood pool imaging.

^{99m}Tc WBCs

A variety of methods are under development for the labeling of white blood cells (WBCs) with ^{99m}Tc. These include Sn^{+2}-reduction methods, in vivo phagocytosis of ^{99m}Tc mini-microspheres or sulfur colloid, and the use of lipid-soluble ^{99m}Tc complexes.

Suggested readings

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Rhodes, B. A.: Considerations in the radiolabeling of albumin, Semin. Nucl. Med. **4:**281-294, 1974.

Stelmach, H. A., and Quinn, J. L., III: Radiopharmaceutical quality control, Semin. Nucl. Med. **4:**295-304, 1974.

Operating a radiopharmacy

Physical setup

A radiopharmacy should be located in a room or building that provides a clean environment: clean with respect to dust and microorganisms and clean with respect to radiation. This means that it should have a clean air supply (filtered air rather than open windows), a radioisotope hood if volatile nuclides like radioiodine or radioxenon are to be handled, a laminar down-flow hood if open preparations are to be made, lead-lined storage bins and refrigerators, radiation monitoring equipment, and measuring devices. The pharmacy should be provided with fire extinguishers, tie-downs for gas cylinders, and special containers for volatile solvents. It should have floors and laboratory furniture that are easily decontaminated. It should be secure from random traffic. Eating, drinking, and smoking should be prohibited in areas where radioactive materials are in use. High-level radiation areas should be segregated from low-level areas; office activities should be segregated from isotope-handling areas. The telephone and intercom installations should be placed to avoid spread of contamination. Dispensing and waste disposal functions should be separated. The overall design should be made with radiation safety and working efficiency as prime considerations. The radiation safety officer should be consulted about the safety considerations of the layout and the equipment.

Essential equipment includes a dose calibrator, radiation survey meter, radiation area monitor, refrigerator and freezer, lead-windowed shield, and lead storage areas. Other key equipment includes a gamma spectrometer with an automatic sample changer, a multichannel analyzer, calculator, lead-shielded generator cabinet, pH meter, and TLC equipment. Closed cabinets for storage of disposable supplies such as needles, syringes, alcohol wipes, and absorbent pads are very useful. Space for storing glassware, reagent kits, and solvents as well as special radioactive waste bins is essential.

Staffing

Quality in a radiopharmacy operation is best approached by having motivated, well-trained individuals who prepare the reagents and dispense the doses. Desirable personal qualities are respect for, but not fear of, radiation; orderliness; cleanliness; and an ability to remain calm under pressure. The staff should appreciate and use to advantage quality control testing and record keeping. The staff should appreciate a check system that assures the elimination of prescription errors before doses leave the premises. The ability to work and communicate with other nuclear medicine personnel is key to a smooth operation. The staff should expect to be involved in troubleshooting and clinical investigations involving radiopharmaceutical defects or suspected adverse reactions. People who do not function well early in the morning should avoid radiopharmacy because most of the action occurs before the nuclear medicine clinics open, which may be as early as 7 A.M. People who do not like housecleaning should also avoid radiopharmacy, since regular cleaning staffs usually do not clean in radioactive areas.

Dispensing of doses

Orders for radiopharmaceuticals are often received orally, either directly or over the phone. Written orders may be the nuclear medicine
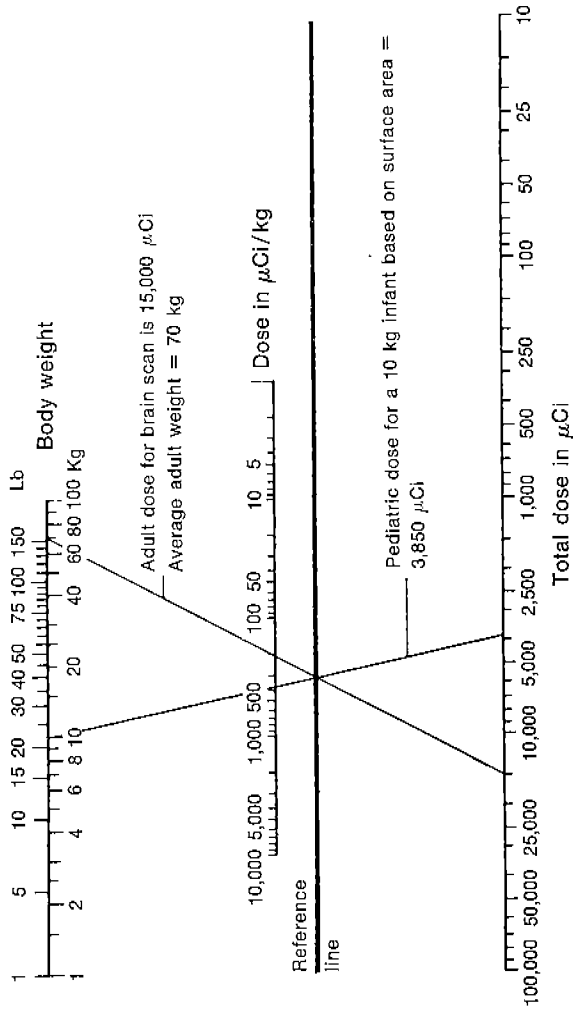
PERCENTAGE OF ADULT
DOSE APPLICABLE TO CHILDREN OF
VARYING WEIGHT BASED ON
SURFACE AREA

Weight		Surface area (meter)	Multiplier for adult dose
Kg	Lb		
3	6.6	0.20	0.12
6	13.2	0.32	0.19
10	22.0	0.46	0.27
20	44.0	0.75	0.44
30	66.0	0.99	0.58
40	88.0	1.21	0.71
50	110.9	1.41	0.83
65	143.0	1.70	1.00

Lb

Body weight

60 80 100 Kg

Adult dose for brain scan is 15,000 μCi
Average adult weight = 70 kg

Dose in μCi/kg

Reference line

Pediatric dose for a 10 kg infant based on surface area =
3,850 μCi

Total dose in μCi

Fig. 12-1. Nomogram for calculating radiopharmaceutical dose for infants and children based on surface area. (From Bell, E. G., McAfee, J. G., and Subramanian, G.: Pediatric nuclear medicine. In James, E. A., Wagner, H. N., Jr., and Cooke, R. E., editors: Radiopharmaceuticals in pediatrics, Philadelphia, 1974, W. B. Saunders Co.)

requisition. It is essential to make sure exactly what study is being planned and which tracer is to be used. The dose is usually established by the indicated protocol. Sometimes, the tracer and the millicurie dose are established by discussion between the physician and the nuclear medicine technologist or radiopharmacist. When more than one protocol is available for a given procedure, the protocol also has to be specified. For example, the dose of ^{99m}Tc SC for a static image with a rectilinear scanner is usually only about a third of that required for a dynamic study using an Anger camera. Also, it is important to know whether the patient is a child or an adult (Fig. 12-1 gives a method of calculating pediatric dosages).

Labeling of the drawn dose is important and should be designed to minimize dispensing errors. Color-coded labels (Fig. 12-2) often
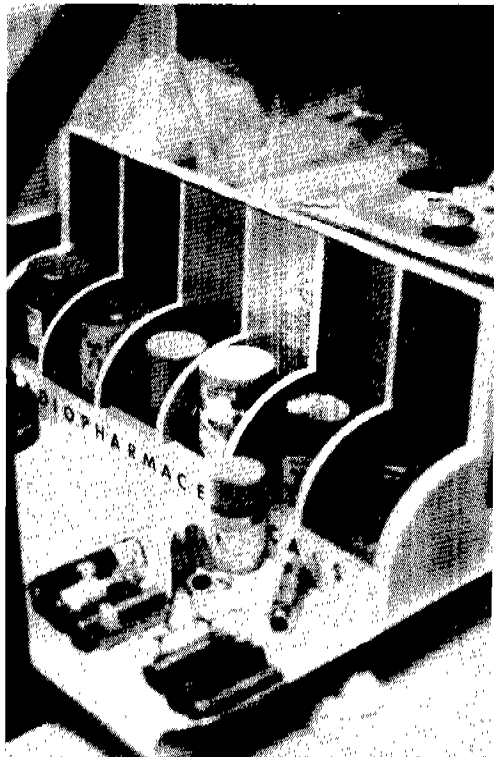
Fig. 12-2. Color-coded vials in their color-matched slots. Color coding aids in differentiation of one radiopharmaceutical from the others and helps to minimize mistakes in drawing doses.

help with this problem. Labeling, however, is a problem; if the label is put on the syringe carrier, it can get separated from the syringe; if it is put on the syringe, it can interfere with the injection or with the placement of the syringe shield. The best solution to this problem is still to be found.

Contamination of paperwork, telephones, syringes, and syringe shields and holders is a universal problem. This is controlled by the proper use of gloves, frequent washing of hands, and repeated monitoring to detect contamination problems before the radioactivity is spread.

Every dose of a radioactive radiopharmaceutical should be checked in a dose calibrator prior to administration to a patient. If the clinic is located some distance from the radiopharmacy, recalibration serves as an essential and final quality control check. The reading from the calibrator should agree with the label. If it doesn't, *believe something is wrong and* STOP! *Get a dose known to be correct before proceeding with an injection.*

The needles used to inject radiopharmaceuticals should be sharp. If the needle is dulled when the dose is drawn, it should be changed. However, changing needles alters the calibration and increases the chances of introducing foreign materials into the solution. Mainly, this procedure offers a chance for spreading radioactive contamination. Proper drawing techniques minimize needle dulling.

Economics

As a general principle, the greater the number of doses dispensed, the lower the cost per dose. This occurs because there is less loss of radioactivity to decay and more efficient use of radiopharmaceutical kits.

The actual practice of radiopharmacy is quite varied. The factors to be taken into account are many. The radiopharmacies range in operation from the large central radiopharmacy serving a whole city or even many counties within a state to the small operation in an individual nuclear medicine department run by one or more nuclear medicine technologists. The factors that must be accounted for are cost of the radiopharmaceuticals from the manufacturers, cost

of kits and generators, shipping costs, personnel costs and availability, space that can be allotted to the radiopharmacy, and time to be spent in preparation and testing of radiopharmaceuticals. One must also take into account the period of stability of the products and the questions of precision of preparation when it is carried out by someone who has other duties as his major responsibility. There is also the question of whether the radiopharmacy is to be only a supplier of routine radiopharmaceuticals or whether it will be carrying out and supporting research, including the preparation of new compounds.

The central radiopharmacy is more cost effective because of the economics of scale. In some areas of the country, the radiopharmaceutical manufacturers serve as central radiopharmacies, delivering on demand materials already prepared. In the case of the central radiopharmacy and the manufacturer, the materials have been tested and may be used on receipt. They may be delivered every day with the same specific activity, simplifying dose volume calculations.

In other areas there is no central radiopharmacy. Until some enterprising radiopharmacist starts one, the hospitals in that area must provide for themselves. These radiopharmacies may range in size from one for which a 50 to 100 mCi ^{99}Mo/^{99m}Tc generator is sufficient to a large institution with its own radiopharmacist producing many materials routinely, including a number for research purposes. It is very difficult to prescribe economic operating methods for all of these different situations. Each operator of a radiopharmacy must examine his own situation and try to find the most efficient, safe, and effective method of operation.

Automation

Currently, most record keeping and all drawing of radioactive doses is done by hand. Both of these functions are readily automated. In addition to improving personnel efficiency, automation of drawing doses could greatly reduce radiation exposure to the hands. It is anticipated that both of these functions will be automated in the not-too-distant future in most larger radiopharmacy operations.

Rules and regulations

Licensure to possess and handle radioactivity is obtained from the Nuclear Regulatory Commission (NRC) or a state agency in agreement states. (Some national agencies are listed below.) Institutional radiation safety officers also deal with special problems, such as spills of radioactivity.

State boards of pharmacy have the jurisdiction to license operating radiopharmacies in some states and pharmacists in all states. Manufacturing radiopharmacies come under additional laws, both state and federal, and may also require a state manufacturing license. Radiopharmacies that manufacture IND or NDA products will probably be inspected periodically by the FDA.

The Department of Transportation (DOT) regulates the packaging and transportation of radioactive materials. The Airline Pilots Association (ALPA) decides what materials may be flown on passenger-carrying aircraft. Most radiopharmaceuticals are shipped by the manufacturers on regularly scheduled passenger-carrying aircraft because they can be expected to arrive on time. To ensure the safety of his passengers, each pilot decides what flies on his plane. Some airports have strict surveillance over all shipments and insist on quarantine and special handling for radioactive materials. Because these procedures may impede the rapid

AEC	United States Atomic Energy Commission (now ERDA)
NRC	Nuclear Regulatory Commission
ERDA	Energy Research and Development Agency
EPA	Environmental Protection Agency
DOT	Department of Transportation
NIA	National Institutes of Health
USP	*The United States Pharmacopiea*
NF	*The National Formulary*
ALPA	Airline Pilots Association
SNM	Society of Nuclear Medicine, Inc.
FDA	Food and Drug Administration
BRA	Bureau of Radiological Health
HEW	Department of Health, Education, and Welfare
NBS	National Bureau of Standards

delivery of shipments, it is important to make friends with the authorities.

Record keeping

The essence of the operation of a well-run radiopharmacy is accountability, as evidenced in the records. The records provide a trail from the manufacturer to the patient that can be followed at every step. There should be no unknown steps in the dosing of a patient in the unlikely event that the material injected needs to be traced. Well-kept records can also prevent errors in dosing and allow the recognition of the very occasional manufacturer's error.

Each radiopharmaceutical that is received or prepared must have a separate log entry, along with a record of each dose that is dispensed from the vial in question. Manufacturers supply extra labels to facilitate the keeping of these records. One can simplify the keeping of all this information by having a separate notebook for each material and a separate page (Fig. 12-3) for each individual vial prepared or received. The name of the material, date, quantity at the calibration time, lot number, and generator number, if any, must be kept along with the names of the patients, dates (and perhaps dispensing times), amount dispensed in milliliters and millicuries, and initials of all personnel in-

volved. Quality control information on the material should be included as well. If color coding is used for the vials, labels, and syringes, it should be used in the records. Of course, a record of the dose must be made in the patient's permanent record and in his nuclear medicine department chart. Special labels or stamps may be designed for this purpose.

The radiopharmacy should possess a set of protocols for the nuclear medicine procedures to be sure the correct radiopharmaceuticals and amounts are being used. They should have, as well, a complete set of package inserts for the purchased materials and kits, along with detailed preparation and dispensing instructions, if there are any. Any IND drug production methods and dosage protocols must be strictly adhered to. All these materials should be kept up to date, and the outdated information archived.

Quality control methods should be thoroughly documented. Each method should be written up as a standard protocol, and the dates noted for the time periods when this protocol is applied. Regular checks should be made of the quality control method to make sure that it differentiates the materials as it should.

There should be a regular check of the performance of the instruments being used in the

Fig. 12-3. Rotating file for storing notebooks containing inventory data for each radionuclide.

radiopharmacy. Each piece of equipment should have its own notebook in which regular calibration information, observations, and repairmen's remarks are recorded. The instruments must be in proven good working order to be of any use in the laboratory.

A set of catalogs from the manufacturers should be available in one place, as well as all the information about how to contact a manufacturer with a rush order or a complaint.

Strict inventory records must be kept in order to be sure a material is on hand when it is needed. Documentation of the amounts ordered and prices paid will assist the radiopharmacist in negotiations with the manufacturers for better prices. It will also help in the prediction of future needs for materials, equipment, and space in a field of medicine that is growing so rapidly.

Transportation of radioactive prescriptions

Syringes containing doses of radiopharmaceuticals ready to be administered to patients
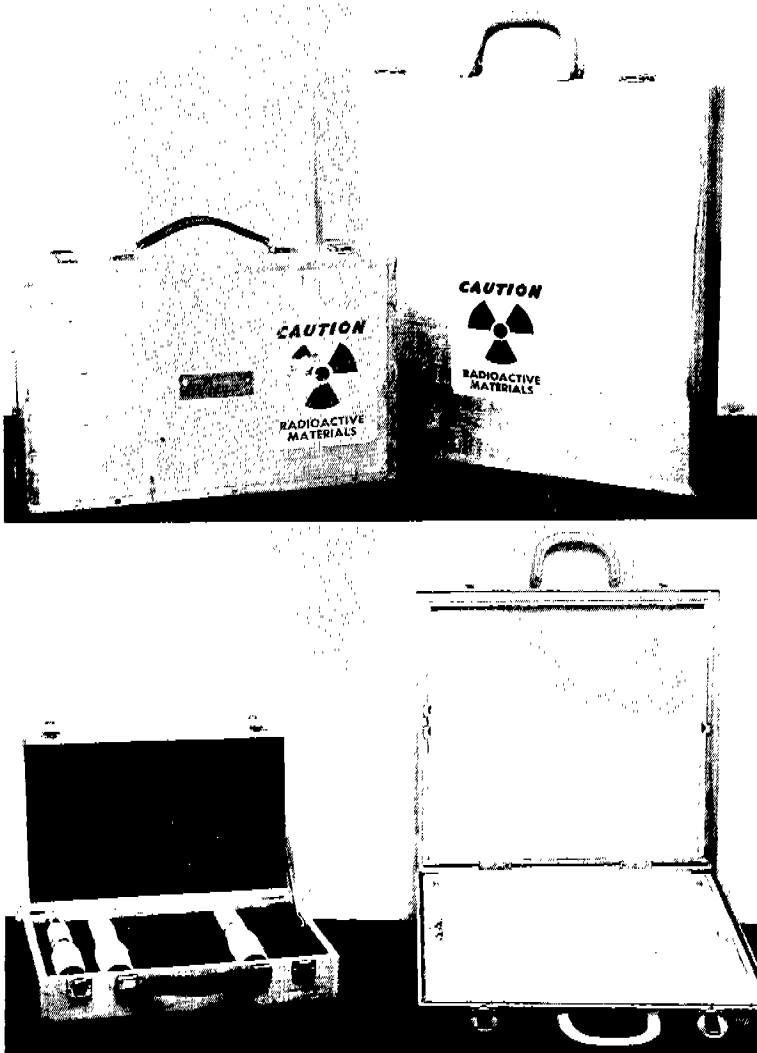
Fig. 12-4. Carrying cases for radioactive doses in syringe shields and for $^{99m}TcO_4^-$-loaded flood field source.

must be transported to their place of administration. Special holders for these syringes have been developed (Fig. 12-4). A similar case has been designed to transport the flood-field source loaded with ^{99m}Tc.

Central radiopharmacies that supply doses to distant clinics often face very challenging transportation problems. Some modes of public transportation can be used, but many carriers are afraid to handle radioactive materials and refuse to cooperate. Education regarding the safety and the importance of these drugs sometimes can be used to gain the cooperation of the carriers. Often a central radiopharmacy will maintain its own fleet of vehicles and staff of drivers.

System quality controls

In addition to the quality control tests for individual compounds listed in Chapter 11, a number of tests can be applied to check the overall quality of the radiopharmacy operation.

Are the drawing techniques aseptic? Spent vials of daily preparations of radiopharmaceuticals should be saved. After the radioactivity has decayed, the contents are pooled and tested for bacterial growth. If growth is found, the handling and transferring methods should be re-evaluated to assure reinstatement of aseptic techniques.

Are working areas clean? Agar plates can be exposed in laminar flow hoods to check the efficiency of bacterial removal. Also, smoke guns can be used to make sure that working methods and equipment in the hoods are not interfering with the laminar flow. The isotope fume hoods should be checked periodically for lack of radioactive contamination and adequate air flow.

Are personnel radiation exposures within accepted limits? Personnel radiation exposures are monitored with film badges. Wrist or finger badges should be used by individuals handling syringes containing radiopharmaceuticals. All workers should get a report of their exposure records. Personnel should be checked for accu-

mulation of radioiodine in their thyroids. Weekly urine samples can be checked for ^{99m}Tc. If ^{99m}Tc is discovered in urine, it indicates that procedures for handling ^{99m}Tc compounds are not adequate and should be modified. ^{99m}TcO$_4^-$ on skin will be absorbed and excreted in the urine. The best time to carry out this test is at the end of the work week.

Is the laboratory being contaminated with radioactivity? Weekly wipe testing around the laboratory should be made to test for such contamination. Telephones, refrigerator and faucet handles, door knobs, radiation shielding, and the floor in front of drawing stations are likely places to be contaminated and should be routinely checked. When contamination is found, spread should be avoided and decontamination procedures instituted. Identification of radionuclides involved is necessary to establish the magnitude of the problem and to decide how to proceed with the decontamination.

Are the nuclear detection devices giving accurate measurements? Routine calibration checks with reference standards are made and recorded for future reference. Is the other equipment working up to par? For example, is the refrigerator used to store heat-sensitive radiopharmaceuticals and other reagents operating at the correct temperature? In summary, the quality control program should cover all aspects of the operation. The results of quality control tests should be used promptly to correct faulty operations.

Suggested readings

Baker, W. J.: Nuclear pharmacy: the regulation of radiopharmacists and radiopharmacies, Proceedings of the 1976 Annual Meeting, District 8, Salt Lake City, Utah, 1976, NABP, AACP.

Kristensen, K., Müller, T., and Rhodes, B. A.: Good radiopharmacy practice. In Rhodes, B. A., editor: Quality control in nuclear medicine: radiopharmaceuticals, instrumentation, and in vitro assays, St. Louis, 1977, The C. V. Mosby Co.

Scheele, R. V., and Wakley, J.: Elements of radiation protection, Springfield, Ill., 1975, Charles C Thomas, Publisher.

Layout of a radiopharmacy

Robert Adams, R.Ph.

The equipping and layout of a radiopharmacy is demonstrated by the following series of photographs; each one of which points out some vital equipment or operation within the standard radiopharmacy.
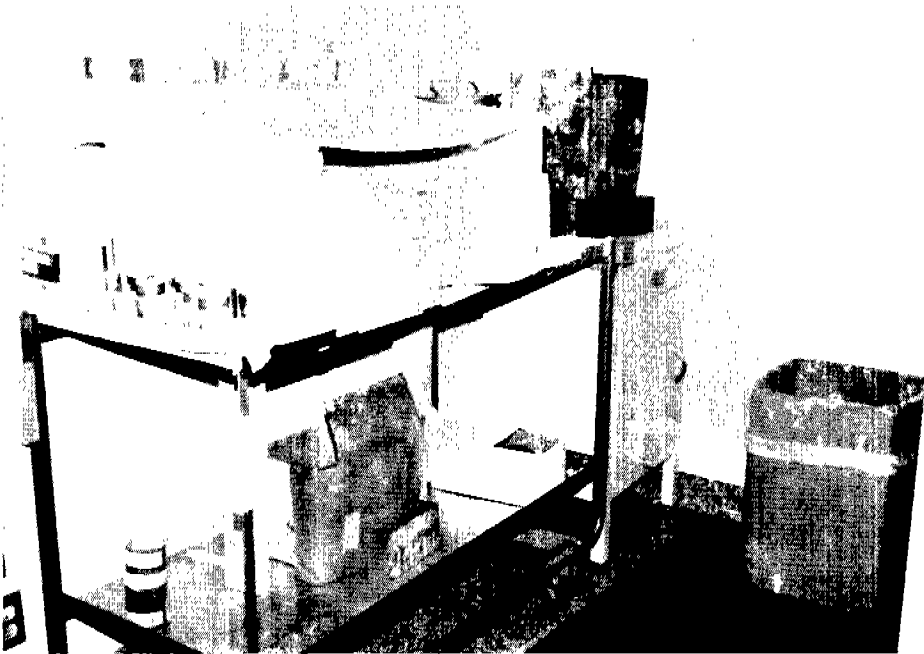
Fig. A-1. Housing for technetium generators enclosed within lead cabinets to provide extra shielding. Note that lead is surrounded by absorbent material so that if leak occurs, absorbent material can be gathered up and discarded without contamination of lead shielding. Because background in area of technetium generators is higher than other areas in radiopharmacy, the generator is usually isolated from other work areas to cut down on radiation exposure to radiopharmacist.
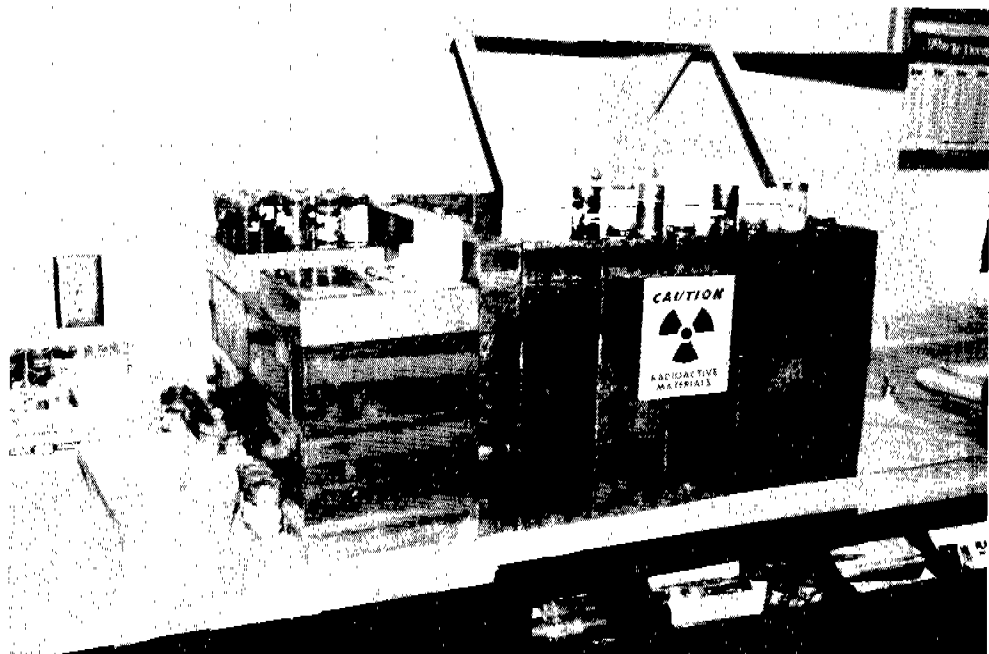
Fig. A-2. Lead housing for freshly prepared radiopharmaceuticals. Lead window allows radio-pharmacist to observe radiopharmaceuticals contained within shield. Radiopharmaceuticals are kept inside lead pigs that are stored inside lead housing and are only removed from this area when doses are being drawn. Also located inside lead housing is lead box used for temporary storage of such radioactively contaminated materials as syringes, needles, and alcohol swabs that are used during product-compounding and dose-dispensing processes.
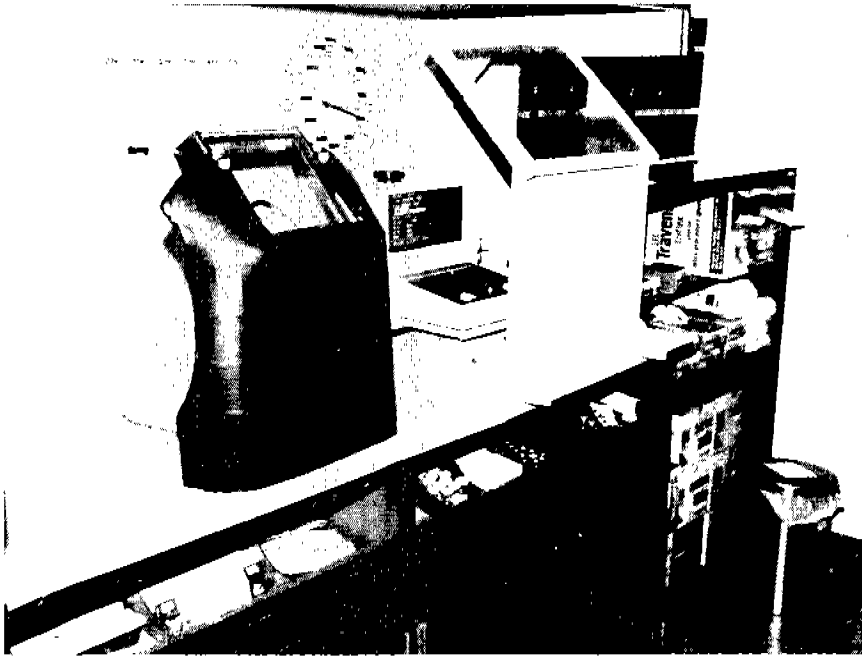
Fig. A-3. Radiopharmaceutical drawing station. When dose is dispensed, container with radio-pharmaceutical is removed from storage area shown in Fig. A-2 and transferred behind lead shield illustrated here. Dose is then withdrawn into syringe, and actual radioactivity assayed in dose calibrator behind second lead glass shield. This operation is set up in laminar flow bench in order to assure sterility of transfer operation. Also note that sterile syringes, needles, and vials are immediately available for making transfers.

Fig. A-4. Lead-lined refrigerator for radioisotope and radiopharmaceutical kit storage.
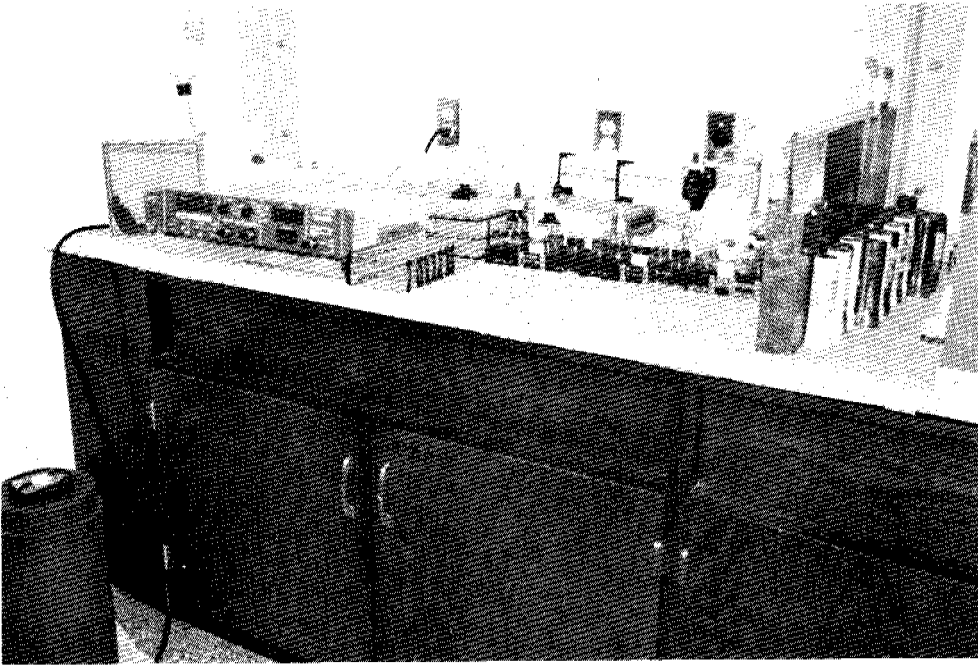
Fig. A-5. Special isolated area in radiopharmacy is used for quality control testing of freshly prepared radiopharmaceuticals.
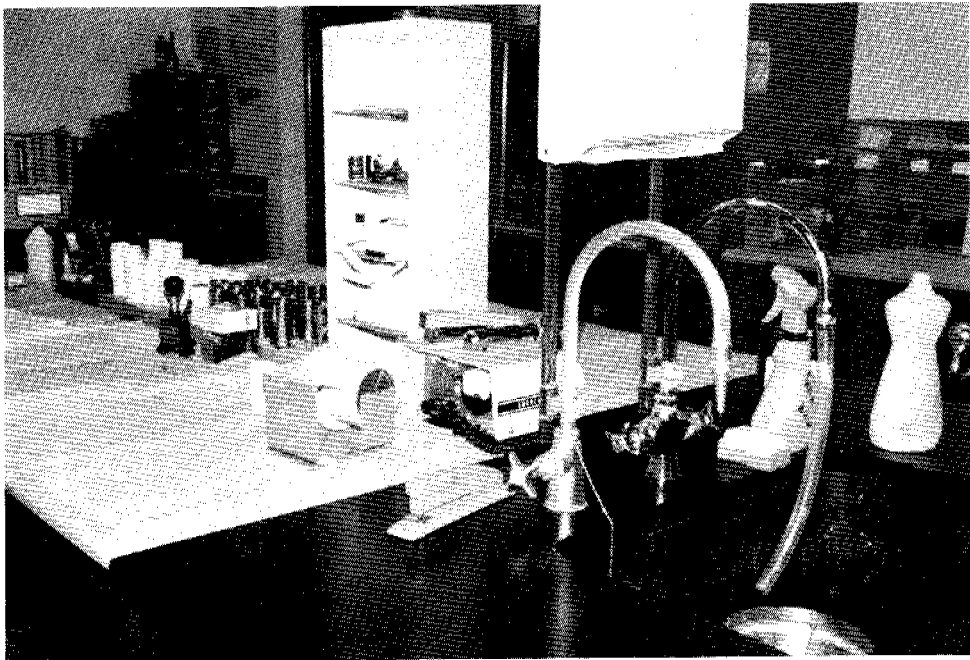
Fig. A-6. Radiopharmacies should be equipped with sink area for washing hands after handling radioactive materials. Note that work areas are covered with absorbent paper so that if spillage occurs, cleanup can be simple and immediate. Radiation monitors can be observed next to sink and at far end of bench.

Fig. A-7. Special area used for packaging radiopharmaceuticals for shipment to distant nuclear medicine clinics.
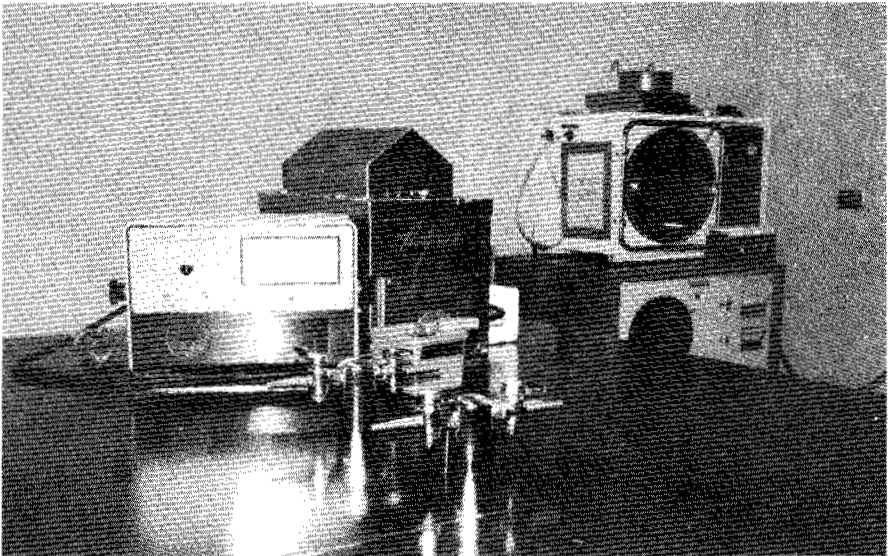
Fig. A-8. Specialty equipment used for preparing and testing radiopharmaceuticals. In background a freeze drier is shown that is used for manufacturing radiopharmaceutical kits. On bench behind radiation monitor is water bath used for incubating samples during Limulus testing for pyrogens.

Fig. A-9. Lead-shielded areas enclosed in a fume hood used for dispensing of volatile radio-pharmaceuticals such as iodide 131 solution and xenon 133 gas. In foreground is radition safety officer monitoring background levels in radioisotope hood.
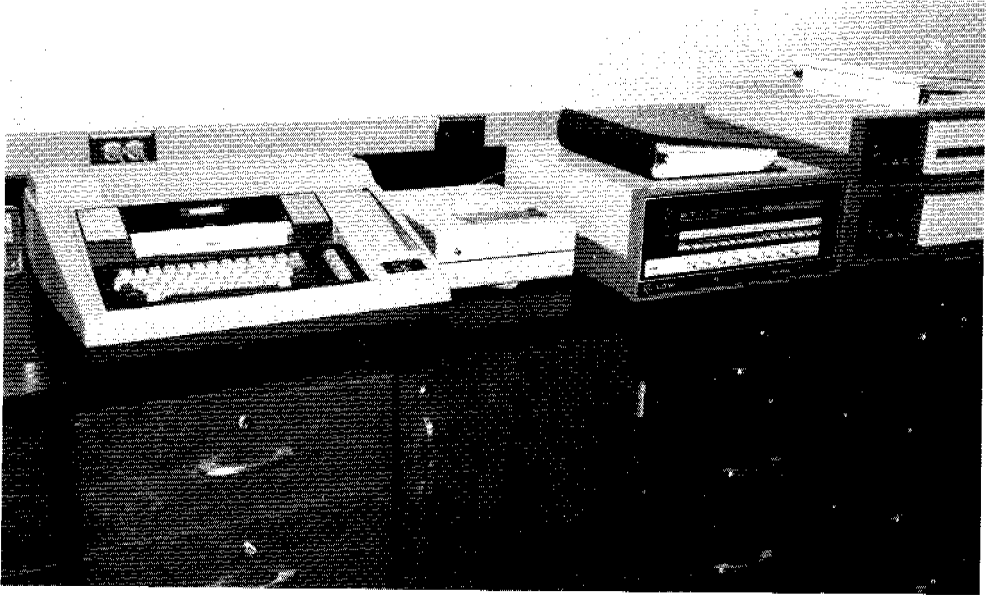
Fig. A-10. Computer equipment used for accounting, quality control record keeping, radioisotope inventory, and decay calculations. A current trend in radiopharmacy is to computerize entire record keeping system.

Fig. A-11. Isolated from rest of activities of radiopharmacy is separate area for storing radioactive wastes until they have decayed or can be transferred into permanent storage. Note in background lead bin for storing such isotopes as gallium 67, iodine 131, and ytterbium 169.

Practical generator kinetics *

Myles Lamson III, M.S., Clifford E. Hotte, Ph.D., and Rodney D. Ice, Ph.D.

Abstract

Equations describing the decay and buildup of nuclides in the ^{99}Mo/^{99m}Tc generator are presented and discussed. The three basic time functions which describe the quantities of ^{99}Mo, ^{99m}Tc, and ^{99}Tc are then manipulated to yield time-dependent factors that simplify the calculations of generator decay. These factors are (1) the fraction of maximum ^{99m}Tc radioactivity at t hours after prior elution, (2) ^{99m}Tc radioactivity as a fraction of ^{99}Mo radioactivity at time t following prior elution, and (3) the mole fraction of total technetium present in the generator as the metastable isomer at time t. These factors allow simple and accurate calculations of relative yields of ^{99m}Tc at different times after prior elution, expected yield in millicuries and generator elution efficiency, and total molar quantity of technetium eluted. Examples are presented. Solutions of the basic differential equations are described in detail in Appendix 1.

Introduction

The ^{99m}Tc ion–exchange generator is one of the primary reasons for the remarkable growth of nuclear medicine during the past decade. In addition to the steadily increasing capabilities of nuclear medical instrumentation, the ready clinical availability of ^{99m}Tc has reduced patient radiation exposures per microcurie by two to three orders of magnitude, increased the avail-

able photon flux in imaging studies, and produced a dramatic reduction in cost per study relative to the radionuclides used previously. The technetium generator has allowed even the smallest of institutions to maintain a continual supply of this short-lived radiopharmaceutical.

The decay kinetics of parent-daughter systems are well known, with one of the earliest descriptions by Rutherford and Soddy in 1902[1]! Even so, the complex exponential relationships needed to describe the decay and buildup of nuclides in the ^{99m}Tc generator are too cumbersome for routine clinical use without the aid of a computer or programmable calculator (see Appendix 2 for HP-67 program). Transient equilibrium is not attained for 2 to 3 days; therefore, an estimate of ^{99m}Tc activity that assumes an equilibrium condition prior to this time is invalid. However, a close examination of the classical decay kinetics indicates certain simple and accurate methods for predicting such parameters as the activity of ^{99m}Tc to be eluted from the generator, the generator elution efficiency, and the total mass of technetium present in an eluate.

Theory

The following differential equations (1 to 3) describe the decay and buildup of nuclides in the technetium generator, where subscripts $_1$, $_2$, and $_3$ refer to ^{99}Mo, ^{99m}Tc, and ^{99}Tc, respectively:

$$\frac{dN_1}{dt} = -\lambda_1 N_1 \qquad N_1(0) = N_1^0 \quad (1)$$

$$\frac{dN_2}{dt} = 0.86\lambda_1 N_1 - \lambda_2 N_2 \qquad N_2(0) = N_2^0 \qquad \textbf{(2)}$$

$$\frac{dN_3}{dt} = 0.14\lambda_1 N_1 + \lambda_2 N_2 \qquad N_3(0) = N_3^0 \qquad \textbf{(3)}$$

The superscript ^{0} in the initial conditions refers to the number of atoms present at time $t = 0$; the quantities N_1, N_2, and N_3 then refer to the numbers of atoms of each respective nuclide at time t. The equations indicate that the time rate of change, $\frac{dN}{dt}$, is proportional to the number of atoms, N. Thus the rate of change equals N times a proportionality constant, or decay constant, λ. The minus sign in equation 1 indicates a decrease in the number of atoms of ^{99}Mo initially present, while the positive term in equation 3 indicates a buildup of ^{99}Tc. (Although ^{99}Tc is radioactive, its $T_{\frac{1}{2}}$ is so long relative to ^{99}Mo and ^{99m}Tc that it is considered stable.) Equation 2 demonstrates a buildup of ^{99m}Tc equal to a fraction of the decay of ^{99}Mo, in addition to its own decay, $-\lambda_2 N_2$. The coefficients of 0.86 and 0.14 are introduced as a result of the branching decay of ^{99}Mo: 86% decays to ^{99m}Tc, while 14% goes directly to ^{99}Tc (see decay scheme in Fig. B-1 and reference 2). The methods for solving these equations, that is, removing the differential terms by integration, are presented in Appendix 1. The solutions of equations 1 to 3 are indicated by equations 4 to 6, respectively:

$$N_1 = N_1^0 e^{-\lambda_1 t} \qquad \textbf{(4)}$$

$$N_2 = N_2^0 e^{-\lambda_2 t} + 0.86 N_1^0 \frac{\lambda_1}{\lambda_2 - \lambda_1} (e^{-\lambda_1 t} - e^{-\lambda_2 t}) \quad \textbf{(5)}$$

$$N_3 = N_3^0 + N_2^0 (1 - e^{-\lambda_2 t}) + \qquad \textbf{(6)}$$
$$0.86 N_1^0 \left[1 + \frac{\lambda_1}{\lambda_2 - \lambda_1} e^{-\lambda_2 t} - \frac{\lambda_2}{\lambda_2 - \lambda_1} e^{-\lambda_1 t} \right] + 0.14 N_1^0 (1 - e^{-\lambda_1 t})$$

If only ^{99}Mo is present initially, then $N_2^0 = N_3^0 = 0$ and equations 5 and 6 simplify to

$$N_2 = 0.86 N_1^0 \frac{\lambda_1}{\lambda_2 - \lambda_1} (e^{-\lambda_1 t} - e^{-\lambda_2 t}) \qquad \textbf{(7)}$$
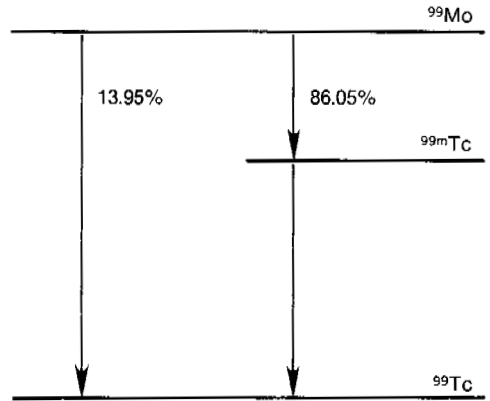
Fig. B-1. Branching decay of ^{99}Mo.
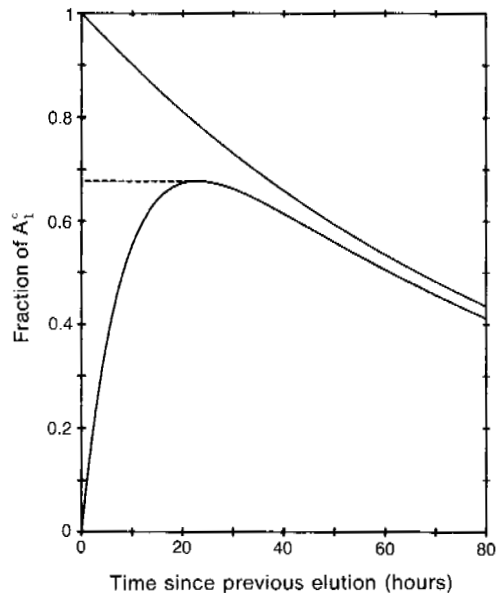
Fig. B-2. Buildup and decay of ^{99m}Tc from ^{99}Mo. Maximum technetium radioactivity is 67.7% of activity of ^{99}Mo at $t = 0$ (time of previous elution).

$$N_3 = 0.86 N_1^0 \left[1 + \frac{\lambda_1}{\lambda_2 - \lambda_1} e^{-\lambda_2 t} - \qquad \textbf{(8)} \right.$$
$$\left. \frac{\lambda_2}{\lambda_2 - \lambda_1} e^{-\lambda_1 t} \right] + 0.14 N_1^0 (1 - e^{-\lambda_1 t})$$

where[3] $\quad \lambda_1 = \dfrac{\ln 2}{66.48 \text{ hr}} = 0.01043 \text{ hr}^{-1}$

$$\lambda_2 = \frac{\ln 2}{6.02 \text{ hr}} = 0.1151 \text{ hr}^{-1}$$
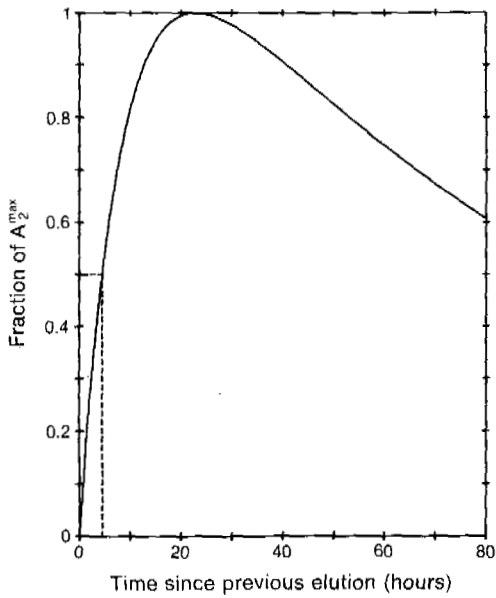
Fig. B-3. Fraction of maximum ^{99m}Tc radioactivity. Technetium activity is 50% of maximum at 4.5 hours after prior elution; A_2^{max} occurs at 22.9 hours.

Table 1. Radioactivity of ^{99m}Tc in generator as fraction of maximum ^{99m}Tc radioactivity

$$f(t) = \frac{0.8605A_1^0\lambda_2\,(e^{-\lambda_1 t} - e^{-\lambda_2 t})}{A_2^{max}(\lambda_2 - \lambda_1)}$$

where $A_2^{max} = 0.677\ A_1^0$

Time (hr)	f(t)	Time (hr)	f(t)	Time (hr)	f(t)
0.5	0.071	10.0	0.817	27	0.992
1.0	0.137	10.5	0.836	28	0.987
1.5	0.200	11.0	0.852	29	0.983
2.0	0.258	11.5	0.868	30	0.977
2.5	0.314	12.0	0.882	32	0.965
3.0	0.365	13.0	0.907	34	0.952
3.5	0.414	14.0	0.928	36	0.937
4.0	0.458	15.0	0.946	38	0.922
4.5	0.501	16.0	0.961	40	0.906
5.0	0.540	17.0	0.973	44	0.874
5.5	0.578	18.0	0.982	48	0.841
6.0	0.612	19.0	0.989	54	0.793
6.5	0.645	20.0	0.994	60	0.746
7.0	0.675	21.0	0.998	66	0.701
7.5	0.703	22.0	0.999	72	0.659
8.0	0.729	23.0	1.000	78	0.619
8.5	0.754	24.0	0.999	84	0.582
9.0	0.776	25.0	0.998	90	0.546
9.5	0.798	26.0	0.995	96	0.513

In the following section relationships are derived that allow tabulation of several time-dependent kinetic factors. These factors in turn permit simple calculation of basic stoichiometric data regarding the technetium generator. The only information needed for these calculations is the calibration activity of ^{99}Mo and the time elapsed between generator elutions.

Applications

Three important questions about available technetium can be answered by manipulating these basic decay equations to yield time-dependent kinetic factors. The first question is "How long after a prior elution is the radioactivity of ^{99m}Tc in the generator maximized?" A related question is "What is the ^{99m}Tc activity at various times as a fraction of this maximum activity?" The first step necessary to answer these questions is to multiply both sides of equation 7 by λ_2 to give units of disintegrations per second (A) rather than atoms (N):

$$\lambda_2 N_2 = 0.86 N_1^0 \frac{\lambda_1 \lambda_2}{\lambda_2 - \lambda_1}\,(e^{-\lambda_1 t} - e^{-\lambda_2 t})$$

Since $A = \lambda N$,

$$A_2 = 0.86 A_1^0 \frac{\lambda_2}{\lambda_2 - \lambda_1}\,(e^{-\lambda_1 t} - e^{-\lambda_2 t}) \quad \text{(9)}$$

A graph of the decay of ^{99}Mo (equation 4) and the buildup and decay of ^{99m}Tc (equation 9) is shown in Fig. B-2. Setting the first derivative with respect to time equal to zero and solving for t yields t_{max}:

$$\frac{dA_2}{dt} = \frac{0.86 A_1^0 \lambda_2^2}{\lambda_2 - \lambda_1}e^{-\lambda_2 t} - \frac{0.86 A_1^0 \lambda_1 \lambda_2}{\lambda_2 - \lambda_1}e^{-\lambda_1 t} = 0$$

$$\frac{0.86 A_1^0 \lambda_2^2}{\lambda_2 - \lambda_1}e^{-\lambda_2 t} = \frac{0.86 A_1^0 \lambda_1 \lambda_2}{\lambda_2 - \lambda_1}e^{-\lambda_1 t}$$

$$e^{-\lambda_1 t}/e^{-\lambda_2 t} = \lambda_2/\lambda_1$$

$$e^{t(\lambda_2 - \lambda_1)} = \lambda_2/\lambda_1$$

$$t(\lambda_2 - \lambda_1) = \ln(\lambda_2/\lambda_1)$$

$$t_{max} = \frac{\ln(\lambda_2/\lambda_1)}{\lambda_2 - \lambda_1} = 22.9\ \text{hr}$$

The maximum activity of ^{99m}Tc is present in

the generator at 22.9 hours following prior elution. Using equation 9, if $t = t_{max} = 22.9$ hours, then solving for A_2 yields the maximum activity of ^{99m}Tc as a fraction of the initial activity of ^{99}Mo. A_2^{max} is thus equal to $0.677 A_1^0$. By substituting various time intervals into equation 9 and dividing by A_2^{max}, the fraction of the maximum activity of ^{99m}Tc present at any time following prior elution is determined. This function is:

$$f(t) = \frac{0.86 A_1^0 \lambda_2 (e^{-\lambda_1 t} - e^{-\lambda_2 t})}{A_2^{max} (\lambda_2 - \lambda_1)} \quad (10)$$

The equation was evaluated at several values of t and the resultant data are presented in Table 1 and Fig. B-3. The f(t) factor allows one to determine relative activities of ^{99m}Tc on the column at various times (example 1, p. 168). Note that within 2 hours after prior elution, 25% of the maximum ^{99m}Tc radioactivity is regenerated.

A second question regarding the $^{99}Mo/^{99m}Tc$ system is "What is the radioactivity of ^{99m}Tc as a fraction of ^{99}Mo radioactivity after any time t?" This information allows the calculation of elution efficiency as well as the expected yield of ^{99m}Tc, based on the calibration activity of ^{99}Mo. The function g(t) is equal to A_2 (equation 7 multiplied by λ_2) divided by A_1 (equation 4 multiplied by λ_1) and reduces to:

$$g(t) = \frac{A_2}{A_1} = \frac{0.86 \lambda_2 (e^{-\lambda_1 t} - e^{-\lambda_2 t})}{(\lambda_2 - \lambda_1)(e^{-\lambda_1 t})} \quad (11)$$

The limit of this function as t becomes very large is:

$$\lim_{t \to \infty} g(t) =$$

$$\lim_{t \to \infty} \left[\frac{\lambda_2 (0.86) - \lambda_2 (0.86)(e^{-\lambda_2 t}/e^{-\lambda_1 t})}{\lambda_2 - \lambda_1} \right] =$$

$$\frac{\lambda_2 (0.86)}{\lambda_2 - \lambda_1} = 0.946$$

When t is large, for example, greater than approximately 2 to 3 days, the radioactivity of ^{99m}Tc becomes a constant fraction of the ^{99}Mo radioactivity (0.946) and decreases with the half-life of ^{99}Mo; this is known as transient

Table 2. Radioactivity of ^{99m}Tc in generator as fraction of present ^{99}Mo radioactivity

$$g(t) = \frac{A_2}{A_1} = \frac{0.8605 \lambda_2 (e^{-\lambda_1 t} - e^{-\lambda_2 t})}{(\lambda_2 - \lambda_1)(e^{-\lambda_1 t})}$$

Time (hr)	g(t)	Time (hr)	g(t)	Time (hr)	g(t)
0.5	0.048	10.0	0.614	27	0.890
1.0	0.094	10.5	0.631	28	0.896
1.5	0.138	11.0	0.647	29	0.901
2.0	0.179	11.5	0.662	30	0.905
2.5	0.218	12.0	0.677	32	0.913
3.0	0.255	13.0	0.704	34	0.919
3.5	0.290	14.0	0.728	36	0.924
4.0	0.324	15.0	0.750	38	0.929
4.5	0.356	16.0	0.769	40	0.932
5.0	0.386	17.0	0.787	44	0.937
5.5	0.414	18.0	0.803	48	0.940
6.0	0.441	19.0	0.817	54	0.943
6.5	0.467	20.0	0.830	60	0.944
7.0	0.492	21.0	0.841	66	0.945
7.5	0.515	22.0	0.852	72	0.946
8.0	0.537	23.0	0.861	78	0.946
8.5	0.558	24.0	0.870	84	0.946
9.0	0.578	25.0	0.877	90	0.946
9.5	0.596	26.0	0.884	96	0.946

Fig. B-4. Radioactivity of ^{99m}Tc as fraction of ^{99}Mo radioactivity. Transient equilibrium is demonstrated as technetium activity approaches constant fraction of molybdenum activity (0.946), 2 to 3 days after previous elution.

:quilibrium. Function g(t) was evaluated versus ime. The data are presented in Table 2 and displayed graphically in Fig. B-4. With the radioactivity of ^{99}Mo from the stated calibration activity, this factor allows one to calculate the present radioactivity of ^{99m}Tc in the generator. Comparing this with the eluted radioactivity yields the elution efficiency (examples 2 and 3, p. 168).

A third question answered by the basic kinetic equations (4, 7, and 8) is "How much of the technetium in a generator is present as the metastable isomer?" Another manipulation of the equations allows one to prepare a table of 99m mole fractions at various times following prior elution, that is, the fraction of the total molar quantity of technetium which is present as 99m. Thus the total quantity of technetium can be calculated from a knowledge of 99m radioactivity in the eluate and the time elapsed between elutions.[4] The function describing the mole fraction, h(t), is simply the number of atoms of ^{99m}Tc divided by the total number of atoms of technetium (both the metastable and ground-state isomers), and reduces to:

$$h(t) = \frac{N_2}{N_{total}} = \frac{N_2}{N_2 + N_3} = \qquad (12)$$

$$\frac{\lambda_1(e^{-\lambda_1 t} - e^{-\lambda_2 t})}{1.162(\lambda_2 - \lambda_1)(1 - e^{-\lambda_1 t})}$$

This function was also evaluated versus time; results are shown in Table 3 and Fig. B-5. The mole fraction is undefined at $t = 0$ (the denominator is zero when $t = 0$), but by using l'Hôpital's rule it can be shown that the limit of h(t) as t approaches zero is 0.8605. This is another way of arriving at the branching ratio and restates the fact that the first ^{99}Mo nucleus to decay after $t = 0$ has an 86% probability of going to the metastable isomer. Since $N_{total} = N_{99m}/h(t)$ and $A_{99m} = \lambda_{99m}N_{99m}$, then

$$N_{total} = \frac{A_{99m}}{[h(t)](\lambda_{99m})}$$

The total number of atoms of technetium in an eluate can be calculated from the activity of

Table 3. Mole fraction of technetium in generator as metastable isomer

$$h(t) = \frac{N_2}{N_{total}} = \frac{\lambda_1(e^{-\lambda_1 t} - e^{-\lambda_2 t})}{1.162(\lambda_2 - \lambda_1)(1 - e^{-\lambda_1 t})}$$

Time (hr)	h(t)	Time (hr)	h(t)	Time (hr)	h(t)
0.5	0.836	10.0	0.506	27	0.248
1.0	0.813	10.5	0.494	28	0.239
1.5	0.790	11.0	0.482	29	0.231
2.0	0.768	11.5	0.471	30	0.223
2.5	0.747	12.0	0.460	32	0.209
3.0	0.727	13.0	0.439	34	0.196
3.5	0.707	14.0	0.419	36	0.184
4.0	0.688	15.0	0.401	38	0.173
4.5	0.670	16.0	0.384	40	0.163
5.0	0.653	17.0	0.367	44	0.146
5.5	0.636	18.0	0.352	48	0.131
6.0	0.619	19.0	0.338	54	0.113
6.5	0.603	20.0	0.324	60	0.098
7.0	0.588	21.0	0.311	66	0.086
7.5	0.573	22.0	0.299	72	0.077
8.0	0.559	23.0	0.288	78	0.068
8.5	0.545	24.0	0.277	84	0.061
9.0	0.532	25.0	0.267	90	0.055
9.5	0.519	26.0	0.257	96	0.050
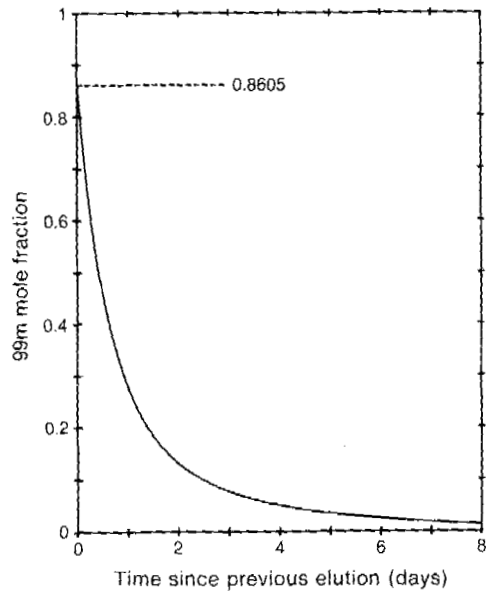
Fig. B-5. 99m mole fraction as function of time. This allows calculation of total molar quantity of technetium in eluate based on A_2 and time since previous elution. Since first ^{99}Mo nucleus to decay after $t = 0$ has 86% probability of decaying to ^{99m}Tc, mole fraction approaches 0.8605 as t approaches zero.

Table 4. Molybdenum-99 decay factors

Factor $= e^{-\lambda_i t}$

Time (hr)	Factor	Time (hr)	Factor	Time (hr)	Factor
−168	5.76	−48	1.65	36	0.687
−144	4.49	−44	1.58	40	0.659
−124	3.64	−40	1.52	44	0.632
−120	3.49	−36	1.46	48	0.606
−116	3.35	−32	1.40	52	0.581
−112	3.22	−28	1.34	56	0.558
−108	3.08	−24	1.28	60	0.535
−104	2.96	−20	1.23	64	0.513
−100	2.84	−16	1.18	68	0.492
−96	2.72	−12	1.13	72	0.472
−92	2.61	−8	1.09	96	0.368
−88	2.50	−4	1.04	120	0.286
−84	2.40	0	1.00	144	0.223
−80	2.30	4	0.959	168	0.174
−76	2.21	8	0.920	192	0.135
−72	2.12	12	0.882	216	0.105
−68	2.03	16	0.846	240	0.082
−64	1.95	20	0.812	264	0.064
−60	1.87	24	0.779	288	0.050
−56	1.79	28	0.747	312	0.039
−32	1.72	32	0.716	336	0.030

99m and from the 99m mole fraction, which is based on time elapsed since prior elution. (Example 4 below illustrates this calculation.) The number of moles (N_{total} divided by **Avogadro's number**) multiplied by the atomic weight gives the mass of technetium in solution.

Examples

1. On Friday night a technologist is called to do a lung scan and elutes the generator at 9 P.M. Several patients are scheduled for studies on Saturday, and as much radioactivity as possible is needed. If the technologist waited until 10 A.M. to elute the generator rather than eluting at 7 A.M., by what percentage would the yield be increased?

	f(t) from Table 1
9 P.M.-7 A.M. = 10 hr	0.817
9 P.M.-10 A.M. = 13 hr	0.907

$$\frac{0.907 - 0.817}{0.817} \times 100 = 11\%$$

The yield of a 10 A.M. elution will be 11% greater than at 7 A.M. However, note in Table 1 that if it is eluted at 7 A.M., the ^{99m}Tc in the generator will be back to 36% of maximum activity at 10 A.M., if more activity is needed.

2. How many millicuries of ^{99m}Tc will you expect to elute from the generator at 8 A.M. Friday morning, assuming 95% elution efficiency, if the prior elution was at 8 A.M. Thursday? The molybdenum is calibrated for 200 mCi at noon Friday. Friday at 8 A.M. is 4 hours prior to calibration time, so from Table 4 (^{99}Mo decay factors):

$$A_{99Mo} = (200 \text{ mCi}) (1.04) = 208 \text{ mCi}$$

From Table 2, after 24 hours the ^{99m}Tc radioactivity is 0.870 of ^{99}Mo radioactivity:

$$(208 \text{ mCi}) (0.870) = 181 \text{ mCi}$$

With 95% elution efficiency, the yield would be approximately 172 mCi eluted from the column.

3. A generator is eluted daily at 8 A.M. On Thursday morning 442 mCi are washed from the column. The molybdenum is calibrated for 400 mCi at noon Friday. What is the elution efficiency? Thursday at 8 A.M. is 28 hours prior to calibration time of the molybdenum; therefore there are 536 mCi of molybdenum on the column:

$$A_{99Mo} = (400 \text{ mCi}) (1.34) = 536 \text{ mCi}$$

The generator is being eluted at 24-hour intervals, so from Table 2, g(t) = 0.870.

$$(536 \text{ mCi}) (0.870) = 466 \text{ mCi } ^{99m}\text{Tc on the column}$$

Therefore, elution efficiency = 442/466 × 100 = 95%. One should be aware, however, that there may be some inaccuracy in generator calibrations and dose calibrator readings.[5]

4. Similarly, what is the total mass (grams) of technetium present in the eluate that contained 442 mCi of ^{99m}Tc at the time of elution?

$$h(t) \text{ at 24 hr} = 0.277$$

$$N_{total} = \frac{A_2}{[h(t)] \lambda_2}$$

$$= \frac{(442 \text{ mCi}) (3.7 \times 10^7 \text{ dps/mCi}) (3,600 \text{ sec/hr})}{(0.277) (0.1151 \text{ hr}^{-1})}$$

$$= 1.85 \times 10^{15} \text{ atoms}$$

$$\frac{1.85 \times 10^{15} \text{ atoms}}{6.02 \times 10^{23} \text{ atoms/mole}} (99 \text{ gm/mole}) = 0.3 \text{ } \mu g$$

Conclusion

As illustrated in the previous examples, the factors presented in Tables 1 through 4 allow simple and accurate calculation of various parameters in regard to the ^{99}Mo/^{99m}Tc generator.

The information on these tables obviates the need to calculate the appropriate kinetic factors by hand and yet provides the requisite accuracy necessary for nuclear medicine procedures. Alternatively, the equations may be evaluated when necessary with the aid of a computer or programmable calculator.

References

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Appendix 1: solution of differential equations describing decay and buildup of nuclides in technetium generator

Equations 1 to 3 are linear first-order differential equations and are readily solved by multiplying by the appropriate integrating factor prior to integration or by separating variables.

EQUATION 1

$$dN_1/dt = -\lambda_1 N_1$$

$$N_1(0) = N_1^0$$

$$dN_1/dt + \lambda_1 N = 0$$

Multiplying by the integrating factor $e^{\lambda_1 t}$:

$$(dN_1/dt)e^{\lambda_1 t} + \lambda_1 N_1 e^{\lambda_1 t} = 0$$

The left-hand side is now the derivative of $N_1 e^{\lambda_1 t}$:

$$D(N_1 e^{\lambda_1 t}) = 0$$

Integrating both sides gives

$$N_1 e^{\lambda_1 t} = C \qquad \textbf{(1a)}$$

By the initial condition, when $t = 0$, $N_1 = N_1^0$. Solving for the constant of integration C:

$$C = N_1^0 e^{\lambda_1 (0)} = N_1^0$$

Substituting back into equation 1a and rearranging yields

$$N_1 e^{\lambda_1 t} = N_1^0$$

or

$$N_1 = N_1^0 e^{-\lambda_1 t} \qquad \textbf{(4)}$$

EQUATION 2

$$\frac{dN_2}{dt} = 0.86\lambda_1 N_1 - \lambda_2 N_2 \qquad N_2(0) = N_2^0$$

Substituting in the expression derived for N_1 yields

$$\frac{dN_2}{dt} = 0.86\lambda_1 N_1^0 e^{-\lambda_1 t} - \lambda_2 N_2$$

By rearranging:

$$\frac{dN_2}{dt} + \lambda_2 N_2 = 0.86\lambda_1 N_1^0 e^{-\lambda_1 t}$$

Multiplying by the integrating factor $e^{\lambda_2 t}$ gives

$$\left(\frac{dN_2}{dt}\right) e^{\lambda_2 t} + \lambda_2 N_2 e^{\lambda_2 t} = 0.86\lambda_1 N_1^0 e^{(\lambda_2 - \lambda_1)t}$$

The left-hand side is now the derivative of $N_2 e^{\lambda_2 t}$:

$$D(N_2 e^{\lambda_2 t}) = 0.86\lambda_1 N_1^0 e^{(\lambda_2 - \lambda_1)t}$$

Integrating both sides and rearranging yields

$$N_2 e^{\lambda_2 t} = 0.86\lambda_1 N_1^0 \int^t e^{(\lambda_2 - \lambda_1)x} dx + C$$

$$N_2 e^{\lambda_2 t} = 0.86\lambda_1 N_1^0 \left[\frac{e^{(\lambda_2 - \lambda_1)t}}{\lambda_2 - \lambda_1}\right] + C$$

$$N_2 = (0.86\lambda_1 N_1^0)\left[\frac{e^{-\lambda_1 t}}{\lambda_2 - \lambda_1}\right] + Ce^{-\lambda_2 t} \quad \textbf{(2a)}$$

By the initial condition, when $t = 0$, $N_2 = N_2^0$. Solving for C:

$$N_2^0 = (0.86\lambda_1 N_1^0)\left(\frac{1}{\lambda_2 - \lambda_1}\right) + C$$

$$C = N_2^0 - 0.86N_1^0\left(\frac{\lambda_1}{\lambda_2 - \lambda_1}\right)$$

By substituting the value of C back into equation 2a and rearranging:

$$N_2 = (0.86\lambda_1 N_1^0)\frac{e^{-\lambda_1 t}}{\lambda_2 - \lambda_1} +$$

$$\left[N_2^0 - 0.86N_1^0\frac{\lambda_1}{\lambda_2 - \lambda_1}\right]e^{-\lambda_2 t}$$

$$N_2 = 0.86N_1^0\frac{\lambda_1}{\lambda_2 - \lambda_1}\, e^{-\lambda_1 t} + N_2^0 e^{-\lambda_2 t} -$$

$$0.86N_1^0\frac{\lambda_1}{\lambda_2 - \lambda_1}\, e^{-\lambda_2 t}$$

$$\textbf{(5)}$$

$$N_2 = N_2^0 e^{-\lambda_2 t} + 0.86N_1^0\frac{\lambda_1}{\lambda_2 - \lambda_1}(e^{-\lambda_1 t} - e^{-\lambda_2 t})$$

EQUATION 3

$$\frac{dN_3}{dt} = 0.14\lambda_1 N_1 + \lambda_2 N_2 \qquad N_3(0) = N_3^0$$

Substituting in the expressions for N_1 and N_2:

$$\frac{dN_3}{dt} = 0.14\lambda_1 N_1^0 e^{-\lambda_1 t} +$$

$$\lambda_2\left[N_2^0 e^{-\lambda_2 t} + 0.86 N_1^0 \frac{\lambda_1}{\lambda_2 - \lambda_1}(e^{-\lambda_1 t} - e^{-\lambda_2 t})\right]$$

This equation is solved by separating variables:

$$dN_3 = 0.14\lambda_1 N_1^0 e^{-\lambda_1 t}dt + \lambda_2 N_2^0 e^{-\lambda_2 t}dt +$$

$$0.86 N_1^0 \frac{\lambda_1 \lambda_2}{\lambda_2 - \lambda_1}(e^{-\lambda_1 t} - e^{-\lambda_2 t})dt$$

Integrating both sides yields

$$N_3 = -0.14 N_1^0 e^{-\lambda_1 t} - N_2^0 e^{-\lambda_2 t} + \qquad \textbf{(3a)}$$

$$0.86 N_1^0 \frac{\lambda_1 \lambda_2}{\lambda_2 - \lambda_1}\left[\frac{e^{-\lambda_2 t}}{\lambda_2} - \frac{e^{-\lambda_1 t}}{\lambda_1}\right] + C$$

By the initial conditions, when $t = 0$, $N_3 = N_3^0$. Solving for C:

$$N_3^0 = -0.14 N_1^0 - N_2^0 +$$

$$0.86 N_1^0 \frac{\lambda_1 \lambda_2}{\lambda_2 - \lambda_1}\left[\frac{1}{\lambda_2} - \frac{1}{\lambda_1}\right] + C$$

$$= -0.14 N_1^0 - N_2^0 +$$

$$0.86 N_1^0\left[\frac{\lambda_1}{\lambda_2 - \lambda_1} - \frac{\lambda_2}{\lambda_2 - \lambda_1}\right] + C$$

$$= -0.14 N_1^0 - N_2^0 + 0.86 N_1^0\left[\frac{\lambda_1 - \lambda_2}{\lambda_2 - \lambda_1}\right] + C$$

$$= -0.14 N_1^0 - N_2^0 - 0.86 N_1^0 + C$$

$$C = N_3^0 + N_2^0 + N_1^0$$

Substituting the value for C back into equation 3a and rearranging yields:

$$N_3 = -0.14 N_1^0 e^{-\lambda_1 t} - N_2^0 e^{-\lambda_2 t} +$$

$$0.86 N_1^0\left[\frac{\lambda_1}{\lambda_2 - \lambda_1}e^{-\lambda_2 t} - \frac{\lambda_2}{\lambda_2 - \lambda_1}e^{-\lambda_1 t}\right] +$$

$$N_3^0 + N_2^0 + N_1^0$$

Since $N_1^0 = 0.14 N_1^0 + 0.86 N_1^0$,

$$N_3 = -0.14 N_1^0 e^{-\lambda_1 t} + N_2^0 e^{-\lambda_2 t} +$$

$$0.86 N_1^0\left[\frac{\lambda_1}{\lambda_2 - \lambda_1}e^{-\lambda_2 t} - \frac{\lambda_2}{\lambda_2 - \lambda_1}e^{-\lambda_1 t}\right] +$$

$$N_3^0 + N_2^0 + 0.14 N_1^0 + 0.86 N_1^0$$

$$N_3 = N_3^0 + N_2^0(1 - e^{-\lambda_2 t}) + \qquad \textbf{(6)}$$

$$0.86 N_1^0\left[1 + \frac{\lambda_1}{\lambda_2 - \lambda_1}e^{-\lambda_2 t} - \frac{\lambda_2}{\lambda_2 - \lambda_1}e^{-\lambda_1 t}\right] +$$

$$0.14 N_1^0(1 - e^{-\lambda_1 t})$$

Appendix 2: HP-67 program for technetium generator kinetics

ABSTRACT

Calculates nine generator elution parameters based on one to four input variables. Determines total concentration of Tc in eluate in atoms/milliliter, grams/milliliter, and molarity; ^{99m}Tc activity as a fraction of maximum ^{99m}Tc activity and as a fraction of ^{99}Mo activity; mole fraction of Tc as metastable isomer; elution efficiency and expected yield in millicuries. Required input may be any or all of (1) ^{99m}Tc activity at time of elution, (2) time between elutions, (3) time since ^{99}Mo calibration, or (4) calibrated activity of ^{99}Mo.

USER INSTRUCTIONS

Step	Instructions	Input (data/units)	Keys	Output (data/units)
1	Load side 1 and side 2			
2	Initialize (store constants in R_1-R_6)		A	0.00
3	Enter time since previous elution, t	H.MMSS	B	f(t)
	or			
3	Enter time since previous elution, t	H.MMSS	C	g(t)
	or			
3	Enter time since previous elution, t	H.MMSS	D	h(t)
	or			
3	Enter time since previous elution, t	H.MMSS	ENTER	
	Enter previous elution efficiency	"EE"	ENTER	
	Enter calibrated activity of ^{99}Mo	mCi	ENTER	
	Enter time since ^{99}Mo calibration, t*	H.MMSS	E	mCi yield
	or			
3	Enter time since previous elution, t	H.MMSS	ENTER	
	Enter ^{99m}Tc activity (@ elution), A	mCi/ml	f, a	atoms/ml
	or			
3	Enter time since previous elution, t	H.MMSS	ENTER	
	Enter ^{99m}Tc activity (@ elution), A	mCi/ml	f, b	gm/ml
	or			
3	Enter time since previous elution, t	H.MMSS	ENTER	
	Enter ^{99m}Tc activity (@ elution), A	mCi/ml	f, c	molarity
	or			
3	Enter decay time, t	H.MMSS	ENTER	
	Enter initial activity of ^{99m}Tc, A	mCi or /ml	f, d	$A_{99m_{Tc}}$
	or			
3	Enter time since previous elution, t	H.MMSS	ENTER	
	Enter total mCi of ^{99m}Tc eluted, A	mCi	ENTER	
	Enter calibrated activity of ^{99}Mo	mCi	ENTER	
	Enter time since ^{99}Mo calibration, t*	H.MMSS	f, e	EE

Step	Key entry	Step	Key entry	Step	Key entry	Step	Key entry
001	fLBL A	057	fH←	113	h R↓	169	fH←
002	·	058	STO 7	114	fH←	170	RCL 2
003	7	059	fGSB 4	115	STO 7	171	x
004	8	060	RCL 2	116	fGSB 5	172	CHS
005	7	061	x	117	RCL B	173	g e^x
006	3	062	RCL 0	118	x	174	RCL 9
007	STO 0	063	÷	119	f FIX	175	x
008	·	064	f FIX	120	DSP 1	176	f FIX
009	0	065	DSP 3	121	h RTN	177	DSP 1
010	1	066	h RTN	122	gLBL a	178	h RTN
011·	0	067	f LBL C	123	STO 9	179	gLBL e
012	4	068	fH←	124	h R↓	180	fH←
013	2	069	STO 7	125	fH←	181	STO 8
014	6	070	fLBL 1	126	STO 7	182	h R↓
015	STO 1	071	fGSB 4	127	fLBL 3	183	STO A
016	·	072	RCL 2	128	fGSB 2	184	h R↓
017	1	073	x	129	RCL 2	185	STO 9
018	1	074	RCL 3	130	x	186	h R↓
019	5	075	x	131	RCL 5	187	fH←
020	1	076	RCL 1	132	÷	188	STO 7
021	4	077	RCL 7	133	RCL 9	189	fGSB 5
022	STO 2	078	x	134	÷	190	RCL 9
023	·	079	CHS	135	h 1/x	191	h x↔y
024	8	080	g e^x	136	g SCI	192	÷
025	6	081	÷	137	DSP 2	193	f FIX
026	0	082	f FIX	138	h RTN	194	DSP 3
027	5	083	DSP 3	139	gLBL b	195	h RTN
028	STO 3	084	h RTN	140	STO 9	196	fLBL 4
029	6	085	fLBL D	141	h R↓	197	RCL 1
030	·	086	fH←	142	fH←	198	RCL 7
031	0	087	STO 7	143	STO 7	199	x
032	2	088	fLBL 2	144	fGSB 3	200	CHS
033	2	089	fGSB 4	145	RCL 6	201	g e^x
034	EEX	090	RCL 1	146	x	202	RCL 2
035	2	091	x	147	RCL 4	203	RCL 7
036	3	092	RCL 3	148	÷	204	x
037	STO 4	093	x	149	h ENG	205	CHS
038	1	094	RCL 1	150	DSP 2	206	g e^x
039	·	095	RCL 7	151	h RTN	207	—
040	3	096	x	152	gLBL C	208	RCL 2
041	3	097	CHS	153	STO 9	209	RCL 1
042	2	098	g e^x	154	h R↓	210	—
043	EEX	099	1	155	fH←	211	÷
044	1	100	h x↔y	156	STO 7	212	h RTN
045	1	101	—	157	fGSB 3	213	fLBL 5
046	STO 5	102	÷	158	EEX	214	RCL 1
047	9	103	f FIX	159	3	215	RCL 8
048	8	104	DSP 3	160	x	216	x
049	·	105	h RTN	161	RCL 4	217	CHS
050	9	106	fLBL E	162	÷	218	g e^x
051	0	107	fH←	163	g SCI	219	RCL A
052	6	108	STO 8	164	DSP 2	220	x
053	STO 6	109	h R↓	165	h RTN	221	fGSB 1
054	0	110	STO A	166	gLBL d	222	x
055	h RTN	111	h R↓	167	STO 9	223	h RTN
056	fLBL B	112	STO B	168	h R↓	—	—

Problems

1. We are required to keep a ^{99}Mo/^{99m}TcO$_4^-$ generator in decay for ten half-lives before turning it over to the radiation safety department for disposal.
   a. How many days must the generator be kept after the date of calibration?
   b. What is the activity of the ^{99}Mo left on the column if the initial activity was 600 mCi?

2. a. How much activity of ^{99m}TcO$_4^-$ remains after ten half-lives if the initial activity was 100 mCi?
   b. What percent of the original activity does this represent?

3. If you desire to reconstitute a cold MAA kit with 75 mCi of ^{99m}TcO$_4^-$, and you milk a generator that yields 823 mCi of ^{99m}TcO$_4^-$ in 11.4 ml of saline, how many milliliters of the generator eluate do you need to inject into the shielded MAA vial?

4. If you had q.s.ed. the ^{99m}Tc-MAA kit (problem 3) to 4 ml with normal saline, how much volume must you draw into a syringe in order to obtain a patient dose of 4 mCi ^{99m}Tc MAA? (Assume no radioactive decay.)

5. If the reconstituted ^{99m}Tc-MAA kit (problems 3 and 4) contains 5 million MAA particles, how many particles would be injected into the patient for the 4 mCi ^{99m}Tc-MAA dose?

6. A ^{99m}Tc–sulfur colloid kit is prepared at 0900 with 60 mCi of ^{99m}TcO$_4^-$ in a total volume of 7 ml. How many milliliters must be injected into a patient's vein at 1330 to provide a dose of 3 mCi?

7. A nuclear medicine department sets its dosage requirements for a thyroid trapping study at 3 to 5 mCi ^{99m}TcO$_4^-$. A dose of 5 mCi is ordered calibrated for 0800. The patient is delayed and does not present himself for the study until 1215. The physician asks you if there is enough activity remaining to do the study. You tell him that the dose is now worth _____ mCi.

8. What activity is represented by 0.6 ml of ^{75}Se selenomethionine on July 31 if the concentration of radioactivity on June 30 was 100 μCi/ml?

9. A nuclear medicine physician desires to inject his patient with 20 mCi of ^{99m}Tc DTPA at 1300 for a dynamic flow study and brain scan. He requests an injection volume of 1 ml or less to assure a good bolus. Your ^{99m}Tc-DTPA kit was prepared at 1000 with 75 mCi ^{99m}TcO$_4^-$ in a volume of 3 ml.
   a. What volume must you draw?
   b. Do you need to prepare a new kit?

10. You read a vial containing ^{131}I solution for therapy and find that you have 75 mCi on hand. The solution was received 4 days earlier. How much radioactivity was initially received? (T$_{\frac{1}{2}} \approx$ 8 days.)

11. The T$_{\frac{1}{2}}$ of indium 113m is 100 minutes. Calculate the decay constant. $\lambda = 6.93 \times 10^{-3}$ M^{-1}

12. What is the number of atoms needed to produce 1 μCi of activity of ^{113m}In? 3.2×10^8 Atoms

13. What is the weight of 1 mCi of ^{113m}In? 6×10^{-11} gm.

14. 5 ml ^{99}Mo/^{99m}Tc-generator eluate contains 75 mCi of ^{99m}TcO$_4^-$ and 52 μCi of ^{99}Mo breakthrough. If the maximum allowable human dose is 5 μCi of ^{99}Mo, what is the maximum activity of pertechnetate that can be injected based on this criterion alone?

15. In problem 14, what is the maximum volume of ^{99m}TcO$_4^-$ solution that can be injected?

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16. Still considering problems 14 and 15, if you wait 2 hours, what is the maximum activity of $^{99m}TcO_4^-$ that can be injected? (Assume negligible ^{99}Mo decay.)

17. Considering problems 14 to 16, what is the maximum volume of $^{99m}TcO_4^-$ that can be injected?

18. If the intensity (exposure rate) at 2.5 cm from a point source is 256 mr/hr, what is the intensity (exposure rate) at 5 cm from the point source?

19. What is the exposure rate at 20 cm in problem 18?

20. If the exposure rate at 50 cm from a point source is 1 mr/hr, what is the exposure rate at 25 cm?

21. If one doubles the distance from a point source, the exposure drops to _____ the initial value. (Express as a fraction.)

22. If one triples the distance from a point, the exposure drops to _____ the initial value. (Express as a fraction.)

23. Radiopharmacist A transfers a reaction vial from a lead container to a calibrator by holding the top of the vial with his hand; the transfer takes 10 seconds. By doing so, his hand is about 1 cm from the point-source activity. Let us assume his hand is exposed to 500 mr/hr. Radiopharmacist B uses a 16 cm pair of tongs to transfer the same vial; the transfer takes 20 seconds. What dose does radiopharmacist B receive to his hand?

24. A radium source of 40 mCi may be used to calibrate survey meters. How far do we have to be away from the source to calibrate the survey meter at 100 mr/hr?

$$\Gamma = 8.3 \ r/mCi \cdot hr \ at \ 1 \ cm$$

25. If the half-value layer of ^{60}Co is 1.2 cm of lead, how much lead is required to reduce the exposure rate from 2,048 mr/hr to 2 mr/hr?

26. Three half-value layers will reduce exposure from a source to _____ its original value. (Express as a fraction.)

27. How many radioactive atoms remain if 3.7×10^{10} atoms of ^{131}I have decayed during the last 8 days? For $^{99m}TcO_4^-$ after 6 hours?

28. If the physical half-life of tritium oxide is 12.3 years and the biologic half-life of tritium oxide is 10 days, what is the effective half-life of the isotope?

29. If a radionuclide has a physical half-life of 12 days and a biologic half-life of 14 days, what is its effective half-life?

30. If the number of photons emitted from a point source is 10,000 per second, what is the flux at a distance of 5 cm from the point source?

31. What is the flux at 10 cm from the point source (problem 30)?

32. The conclusion that can be drawn from the evaluation of calculations in problems 30 and 31 is that doubling the distance from a point source decreases flux to _____ its original value. (Express as a fraction.)

33. What is the radioactivity of a point source for $^{99m}TcO_4^-$ if the flux is 32 photons/cm²/sec at 5 cm?

34. What is the radioactivity of a point source of ^{131}I if the flux of primary rays is 32 photons/cm²/sec at 5 cm?

35. Assuming a Poisson distribution, how many counts represent 1 standard deviation of 10,000, 1,000, and 100 counts?

36. What percent of the total count rate is represented by 1 standard deviation when the mean count of a sample is 10,000? 1,000? 100?

37. As the count increases, does the percent of the total counts represented by 1 standard deviation increase or decrease?

38. Within how many standard deviations of a mean count of 73,441 is 479?

39. What is the 3 standard deviation interval of a count with a mean of 395,641?

40. If one nanogram of element A decays at a rate of 3.7×10^7 dps, what is the specific activity of 1 microgram?

41. A physician wants all his samples reported to him at a 2–standard deviation confidence level and at no more than a 3% error. What is the minimum number of counts that his technologist must collect?

42. If a physician is willing to accept results with a 2–standard deviation confidence level and a 10% error, what is the mini-

mum number of counts that must be collected?

43. A technologist has 8 hours to count 100 samples for Dr. Hurry. He is a demanding person and requires that his lab results be statistically significant and on time. It takes 30 minutes to gather the samples. The technologist finds that the samples read approximately 5,000 cpm, and the sample control blank is 50 cpm. The most efficient use of the remaining time would be to count each sample for _____ minutes and each blank for _____ minutes.

44. Assume we have 100 reactive Ab (antibody) sites and 1,200 cold Ag (antigens), along with 800 Ag* (radioactive antigens). After equilibrium, what is the bound-to-free ratio?

45. Refer to problem 44. What is the ratio of the bound Ag and bound Ag*?

46. You are asked to run an in vitro T_4 test on a patient sample and choose a competitive protein binding assay. To generate your standard curve, you choose to run tubes containing 0, 5, 10, 15, and 20 μg% of sodium levothyroxine (Synthroid) (T_4) and add *T_4-TBG in each tube that gives 10,000 counts/min. You allow each tube to come to equilibrium, separate the bound T_4* from the free T_4*, and get the following results.

$$0\% \ T_4 = 10,000 \text{ cpm}$$
$$5 \ \mu g\% \ T_4 = 8,000 \text{ cpm}$$
$$10 \ \mu g\% \ T_4 = 5,000 \text{ cpm}$$
$$15 \ \mu g\% \ T_4 = 3,000 \text{ cpm}$$
$$20 \ \mu g\% \ T_4 = 1,000 \text{ cpm}$$

a. Plot the standard curve.
b. A normal value in your area is 5 to 14 μg% T_4. Your patient counts 4,000 cpm. What is his μg% of T_4? Is he in normal range?

47. Assume we have a sample with 3.5×10^4 counts/ml. If we add 1 ml of this to a sample of unknown volume and find that 1 ml of this after mixing gives us a count rate of 625 cpm, what is the volume of the unknown solution?

48. We prepare a technetium-pyrophosphate

kit and wish to run a quality control check on our product with TLC procedure. We spot one strip each for solvents of saline and acetone, separate, and count. Our results are as follows:
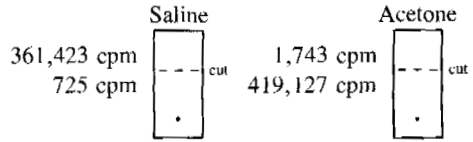
What is the percent hydrolyzed, oxidized, and tag in our product?

49. Given the following data, what is the percent hydrolyzed and percent free $^{99m}TcO_4^-$ in our generator eluate?
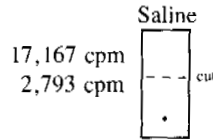
50. A sulfur colloid quality control test gives us the following data. What is the percent oxidized and the percent tag?
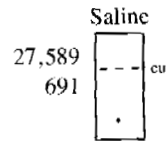
51. A sample of ^{99m}Tc pyrophosphate is injected into the tail vein of a mouse. The injection syringe reads 20 μCi at 1000. At 1200 the injection syringe residual is read at 6.4 μCi. A standard of ^{99m}Tc pyrophosphate is also prepared and reads 18.9 μCi at 1000. This standard is diluted to 2 ml; 0.1 ml of this will be used for comparison with the organ counts. The mouse is sacrificed 4 hours after injection, and the following organs are dissected and counted: heart, stomach, liver, skeleton, muscle, blood, and urine.

a. How much activity was injected into the mouse? The organ system counts obtained are:

Standard	*160,000 cpm*
Heart	50,539 cpm
Stomach	30,324 cpm
Liver	20,216 cpm

Skeleton	1,010,792 cpm
Muscle	60,647 cpm
Blood	40,431 cpm
Urine	808,636 cpm

b. How many counts represent 1 μCi of the standard at sample counting time?

c. How many counts represent 1 μCi of the sample?

d. How many cpm represent 1 μCi initial activity after 5 hours for the standard and sample?

e. Calculate the organ biodistribution for each of the organs listed below. Express answers as (1) total μCi in each organ and (2) percent injected dose per each organ. *Note:* Your organ distributions should add up to 100% of the injected activity in this hypothetical problem.

Heart	_____	_____
Stomach	_____	_____
Liver	_____	_____
Skeleton	_____	_____
Muscle	_____	_____
Blood	_____	_____
Urine	_____	_____

52. If you have 100 ml of a radioactive substance and the concentration is 420 μCi/ml:

a. What would the concentration be if you were to dilute the sample to 140 ml with normal saline?

b. What is the amount of total radioactivity contained in each of the organs mentioned above?

53. Given the following data, calculate the red cell mass.

$$A_{WB1} = 460 \text{ cpm/ml} \left(\frac{1}{200} \text{ dilution}\right)$$

$$A_{WB2} = 340 \text{ cpm/ml (no dilution)}$$

$$A_{P1} = 49 \text{ cpm/ml} \left(\frac{1}{100} \text{ dilution}\right)$$

$$A_{P2} = 30 \text{ cpm/ml (no dilution)}$$

$$Hct_1 = 0.60$$
$$Hct_2 = 0.67$$
$$V_1 = 9 \text{ ml}$$

54. You desire to calculate to patient's plasma volume and inject 10 μCi of ^{125}RISA in 1 ml volume. You take 1 ml patient plasma samples at 10 minutes and 20 minutes after injection and obtain count rates of 2,450 cpm and 2,385 cpm, respectively. Your standard, eluted to 1,000 ml, gives a count rate of 4,872 cpm/ml.

a. Plot the data to find T_0.

b. Calculate the patient's plasma volume.

55. You desire to determine the clearance of 100 μCi of ^{169}Yb DTPA in a rabbit. The dose is injected intravenously, and a probe is placed over the animal's head. Counts obtained over the head are:

3,000 cpm at time of injection
1,800 cpm at 15 minutes
1,100 cpm at 30 minutes
620 cpm at 45 minutes
370 cpm at 60 minutes

a. Plot the data on linear and semilog graph paper.

b. Assuming the drug is cleared only by the kidneys, plot the theoretical radioactivity that would be in the bladder at times 0, 15, 30, 45, and 60 minutes on the graph paper used in part a. (Assume that no urine is passed from the bladder during the course of the study and that once the drug is cleared by the kidneys, it is immediately transferred to the bladder.)

c. What is the approximate time during the study that the amount of isotope is the same in the blood pool and the urine?

d. Calculate K.

e. Using the formula $A_t = A_0 e^{-kt}$, calculate the activity remaining in the blood pool at the times 15 and 45 minutes.

56. The content of one ^{131}I NaI uptake capsule reads 75 μCi and weights 870 mg. This is mixed thoroughly with an unknown amount of powder; a 1-gram aliquot of the combination reads 3.54 μCi. What is the total weight of the powder after mixing?

57. A patient is given a ^{131}I NaI uptake capsule measuring 15 μCi. The patient's thyroid is counted at intervals of 2, 6, and 24 hours. An identical capsule is counted as a control. The net counts obtained are:

Time	Patient	Standard
2 hours	3 312 cpm	54,296 cpm
6 hours	11,314 cpm	52,871 cpm
24 hours	27,973 cpm	49,592 cpm

a. Calculate the percent uptake of the thyroid gland at each time interval.

If the upper range of normal thyroid radioiodine uptake in your geographic area is 20% at 24 hours, if it is decided that this patient is hyperthyroid, and if the patient's physician decides to use ^{131}I solution to ablate the thyroid in order to return the patient to a euthyroid state:

b. Calculate the volume of the gland if the following measurements are made:

Left lobe: r = 1.2 cm, h = 8 cm
Right lobe: r = 1.6 cm, h = 7 cm

c. If the physician decides to give 100 μCi of ^{131}I NaI solution per gram of thyroid, what activity should he administer to the patient? *Hint:* Consider uptake!

58. 1 mCi of ^{131}I MAA delivers a dose of approximately 6.6 rads to the lungs, and 1 mCi of ^{99m}Tc MAA delivers approximately 0.4 rad to the lungs. If the usual dose of ^{131}I MAA is 300 μCi and the usual dose of ^{99m}Tc MAA is 3 mCi, how much of an increase dose is delivered to the lungs if ^{131}I MAA is used instead of ^{99m}Tc MAA?

59. If bone scans with ^{99m}Tc compounds are often performed 3 hours after injection, what is the optimum effective half-life for such a tracer?

60. Consider this hypothetical atom that will decay by electron capture:

Binding energy	Shell
0	
0.4 kev	N shell
1.9 kev	M shell
12.8 kev	L shell
75.0 kev	K shell

a. If an e^- from the L shell fills the hole in the K shell and an e^- from the M shell fills the vacancy created by the L shell, what are the two resultant x-ray energies?

b. If an ambient electron (not in an orbital shell) fills a K shell vacancy, what is the energy of the resultant x ray?

61. Complete the following reactions and list intermediate reaction products.

			Intermediates	Product
a.	$^{113}_{49}$In	(p, n) $\longrightarrow$		
b.	$^{68}_{30}$Zn	(p, 2n) $\longrightarrow$		
c.	$^{111}_{49}$In	electron capture $\longrightarrow$		
d.	$^{40}_{18}$Ar	(α, p) $\longrightarrow$		
e.	$^{45}_{19}$Ca	beta decay $\longrightarrow$		
f.	$^{135m}_{56}$Ba	isomeric transition $\longrightarrow$		
g.	$^{58}_{26}$Fe	(n, α) $\longrightarrow$		
h.	$^{58}_{26}$Fe	(n, p) $\longrightarrow$		

62. Arsenic injection in man will cause acute toxicity symptoms in a dose of 100 mg. If 2 mCi of ^{72}As is used as a brain-scanning agent ($T_{\frac{1}{2}}$ = 26 hours):

a. How many milligrams of arsenic would be injected into a patient?

b. How much activity of ^{72}As represents 100 mg of arsenic?

63. A normal dose of ^{99m}Tc pyrophosphate in a 70 kg man is 20 mCi, which contains 4 mg of pyrophosphate. Calculate on a weight: weight basis the dose for a 20-gram mouse (injected activity and milligram amount of pyrophosphate).

64. A patient is given 150 mCi of ^{131}I solution to treat a thyroid cancer. The urine is collected for 24 hours, and its radioactivity is assayed at 63 mCi. Hospital policy allows the release of a patient when total remaining body activity is 30 mCi or less. If the urine is collected for another 24 hours and measures 41 mCi, how much activity remains in the patient? Can the patient be released from the hospital?

65. The whole-body maximum permissible dose to an adult is 5 rem/yr. How much cumulated exposure is allowed for a 21-year-old radiation worker?

66. How much ^{99m}Tc is present in a ^{99}Mo/ ^{99}TcO$_4^-$ generator 4 hours after a milking if the initial activity of ^{99}Mo was 400 mCi, and 32 mCi of ^{99m}Tc remained on the column after the milking?

67. How many mCi of ^{99m}Tc are on the column

of a ^{99}Mo/^{99m}Tc generator 4 hours after loading by the manufacturer if the amount of ^{99}Mo loaded was 400 mCi? (Assume no ^{99m}TcO$_4^-$ is loaded onto the column.)

68. How long after an elution does it take for the ^{99m}Tc buildup from a ^{99}Mo generator to reach maximum activity?

69. How many mCi of ^{99}Mo remain in a generator 48 hours after calibration if the calibration activity was 550 mCi?

70. 10 mg of ^{127}I$_2$ is subjected to neutron irradiation at a flux of 1×10^9 neutrons/cm^2-sec for a period of 1 hour, thereby forming ^{128}I, which has a T$_{\frac{1}{2}}$ of 25 minutes. The activation cross section is 7 barns.*

a. How much ^{128}I is formed in 1 hour?
b. How much ^{128}I is formed in 3 hours?
c. How much ^{128}I would be formed in 1 hour if the neutron flux were reduced to one half its initial value?
d. How many half-lives are required to produce 50% of the maximum radioactivity at the initial neutron flux?
e. How many half-lives are required to produce 80% of the maximum radioactivity at the initial neutron flux?
f. If a 3-hour irradiation is used and the radioactivity is assayed 3 hours after the end of the irradiation, how much radioactivity is expected?

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* 10^{-24}/cm^2/atom.

Glossary

accelerator Commonly referred to as an "atom smash-er." A device used to impart a high kinetic energy to a charged particle to cause it to undergo nuclear or particle reactions. From the standpoint of the associated "temperature" in the light of the kinetic theory, the accelerator occupies the same position with respect to nuclear reactions that the Bunsen burner occupies in the field of chemical reactions. Common accelerators are the cyclotron, synchrotron, Van de Graff accelerator, and betatron.

acidic Having the characteristics of an acid, that is, a substance which gives hydrogen ion in solution or which neutralizes bases, yielding water. In general, an acid is a molecule with a positive field that is capable of neutralizing a basic molecule having a "free" electron pair.

aerobic Growing only in the presence of molecular oxygen.

aliquot A small but representative and reproducible part of something, such as part of a solution, a sample.

anaphylaxis An unusual or exaggerated reaction of the organism to foreign protein or other substances.

anion A negatively charged ion.

aquation The replacement of coordination groups by water molecules.

aseptic Not septic (alive); free from septic (living) materials.

Avogadro's number The number of molecules in a mole, 6.0228×10^{23}, or the number of atoms in a gram atomic weight.

bacteria (pl.), **bacterium** (s.) In general, any microorganism of the order Eubacteriales; a nonspore-forming, rod-shaped or nonmotile, rod-shaped microorganism. A loosely used generic name for any rod-shaped microorganism, especially enteric bacilli and morphologically similar forms.

bacteriostat An agent that inhibits the growth of bacteria.

basic Having the characteristics of a base, that is, a substance which gives hydroxide ion in solution or which neutralizes acids, yielding water.

biodistribution The distribution of material in a biologic system, such as an experimental animal.

buffer A solution containing large amounts of both a weak acid and a weak base that is able to react with added acid or base, neutralize the added ions, and remain at the original pH.

carrier Stable atoms that are mixed with radioactive atoms of the same element (i.e., same atomic number) in the same chemical form for the purpose of carrying out a chemical process.

carrier free The adjective applied to a nuclide that is essentially free of its stable isotopes.

catalyst A substance that by its presence alters the rate of a reaction and itself remains unchanged at the end of the reaction.

cation A positively charged ion.

channeling (for chromatography columns) During column chromatography, channeling is a process in which liquid flows through a few pathways instead of washing the whole column.

chelate A metal iron attached to a complexing agent at more than one point (i.e., by more than one ligand).

colligative (properties) A property of matter numerically the same for a group of substances, independent of their chemical nature.

collimator An apparatus used to confine radiation to a narrow beam for the purpose of directing that beam or for measuring radiation from an extended source.

colloid A phase dispersed to such a degree that the surface forces become an important factor in determining its properties; the particle size is usually 50 to 500 μ.

complex A compound of two or more parts, in which the constituents are more intimately associated than in a simple mixture.

compounding To form by combining parts, to form a whole, to put together. A pharmacy term describing the making of a drug or radiopharmaceutical.

D_x Medical shorthand for *diagnosis:* the determination of the nature or cause of a disease; also used to indicate a diagnostically useful radiopharmaceutical.

dimer A compound formed by the union of two radicals or two molecules of a simpler compound. More specifically, a polymer formed from two molecules of a monomer.

electrolysis If a current, i, flows for a time, t, and deposits a metal whose electrochemical equivalent is e, the mass, m, of metal deposited is m = eit. The value of e is usually given for mass in grams, i in amperes, and t in seconds.

electron volt (ev) The kinetic energy gained by an electron

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after passing through a potential difference of 1 volt. The electron volt is used to measure the small amounts of energy available from individual nuclear reactions.

element A substance composed entirely of atoms of the same atomic number.

embolus A clot or other plug brought by the blood from another vessel and forced into a smaller one so as to obstruct the circulation.

emulsion A system consisting of a liquid dispersed in an immiscible liquid, usually in droplets of larger than colloid size.

emulsion (photographic) A suspension of a sensitive silver salt or a mixture of silver halides in a viscous medium (as a gelatin solution) forming a coating on photographic plates, film, or paper.

equilibrium, chemical A state of affairs in which a chemical reaction and its reverse reaction are taking place at equal velocities, so that the concentrations of reacting substances remain constant.

free radical A chemical species having one or more unpaired electrons.

fritted glass Smitered (ground glass melted into a porous mat) glass used in filtration.

functional imaging or parametric imaging A derived image formed according to some mathematical rule, as by division of one image by another.

gel A colloid in a solid or semisolid form.

halogens Group 7; the included elements are fluorine, chlorine, bromine, iodine, and astatine, usually with a -1 charge, that is, Cl^-.

hematocrit (Hct) An expression of the volume of the red blood cells per unit volume of circulating blood.

HSA Human serum albumin.

hydrolysis A reaction involving the splitting of water into its ions and the formation of a weak acid, base, or both. A reaction in which water is lost from a complex or chelate.

infarcted (infarct) An area of coagulation necrosis in a tissue due to local anemia resulting from obstruction of circulation to the area.

in situ (Latin) In the natural or normal place; confined to the site of origin without invasion of neighboring tissues.

intrathecal Within a sheath. Applied to the cerebrospinal fluid cavity.

intravenous Within a vein or veins.

in vitro (Latin) Within a glass; observable in a test tube.

in vivo (Latin) Within the living body.

ionization The process of knocking electrons from atoms or molecules, thereby creating ions. High temperatures, electrical discharges, and nuclear radiation can cause ionization.

ischemic (ischemia) Pertaining to a deficiency of blood in a part because of functional construction or actual obstruction of a blood vessel.

isobar One of a group of nuclides having the same total number of particles (neutrons and protons) in the nucleus but with these particles so proportioned as to result in different values of Z; for example, ^3H and ^3He.

isomer (nuclear) One of two or more nuclides with the same number of neutrons and protons in the nucleus (same Z and same A) but existing in different energy states.

isotone Any one of several nuclides with the same number of neutrons in the nucleus but differing in the number of protons.

isotope One of a group of nuclides of the same element (same Z) with the same number of protons in the nucleus but differing in number of neutrons, resulting in different values of A. Sometimes used as a general synonym for nuclide, but this use is not recommended.

kinetics A branch of science that deals with the effects of forces on the motions of material bodies or with changes in a physical or chemical system.

ligand A chemical group, ion, or molecule coordinated to a central atom or group in a complex or chelate.

macroaggregated A particle size of 10 μ and up; this size is used for lung scanning.

mass spectrometer A device for measuring the mass of individual particles by passing them through electrostatic and magnetic fields.

mean transit time The average time for a bolus to pass through a particular organ or area.

metabolism The sum of all physical and chemical processes by which living organized substance is produced and maintained and also the transformation by which energy is made available for the uses of the organism.

metal A substance possessing so-called metallic properties such as electric conductivity, heat conductivity, high reflectivity, and luster, properties due to the high degree of freedom possessed by electrons of the substance.

micelle A unit of structure built up from complex molecules into colloids.

microaggregated A particle size of less than 3 μ used for liver scanning; aggregated denatured albumin.

microsphere A spherical particle usually 1 to 3 μ or 15 to 35 μ in diameter and made from heat-denatured serum albumin.

molarity The concentration of a solute in a solution expressed in molar units, that is, moles of solute per 1,000 ml of solution. One mole is the weight of a substance in grams numerically equal to its molecular weight; a "gram molecule."

mole Synonym for gram molecular weight.

NBS standard A radioactive source standardized and/or certified by the National Bureau of Standards.

neutron activation analysis A method of elemental analysis based on identification of neutron-irradiation products.

normality The concentration of a solute in solution expressed in gram equivalent weights of either acid or base. One gram equivalent weight is equal to the weight of substance necessary to give 1 mole of hydrogen or hydroxyl ions in 1,000 ml of solution.

nuclear magnetic resonance A method for examining the electronic milieu of a nucleus by exciting the nucleus with radio frequencies in a magnetic field.

nuclide A general term referring to any nucleus (stable or radioactive) plus its orbital electrons.

olation Polymerization by the bonding of metal atoms through one or more hydroxyl groups, accomplished by splitting out waters of hydration.

organic (*as it refers to chemicals*) Chemicals composed of a carbon skeleton.

oxalation The conversion of a bridging OH group to a bridging O^{-2} group with the release of hydrogen ions. This process produces insoluble forms of chromium, tin, technetium, and other metal oxides.

oxidation An increase in the oxidation state number of an element; the loss of electrons by an atom or group of atoms.

pH The common logarithm of the reciprocal of the hydrogen ion concentration in moles per liter. It expresses the acidity or alkalinity of a solution, a pH of 7 being neutral. $pH = \log \left[\dfrac{1}{H+} \right]$

palliation (palliative) Affording relief, but not a cure.

parenteral Not through the alimentary canal; for example, by subcutaneous, intramuscular, intraarterial, or intravenous injection.

polymer A chemical compound or mixture of compounds formed by putting together individual units and consisting essentially of repeating structural units.

porphyrin Complex cyclic compounds such as the heme component of hemoglobin.

psychosomatic Pertaining to the mind-body relationship; having bodily symptoms of psychic, emotional, or mental origin.

pyrogen A fever-producing agent usually of bacterial origin (i.e., bacterial endotoxin).

qualitative Relating to, or involving quality or kind. Q. analysis: chemical analysis designed to identify the components of a substance or mixture.

quantitative Relating to, or involving the measurement of quantity or amount. Qu. analysis: chemical analysis designed to determine the amounts or proportions of the components of a substance.

R$_x$ Symbol for Latin *recipe*, hence used as a symbol for therapy; also used to indicate a therapeutically useful radiopharmaceutical.

rad Radiation absorbed dose: the basic unit of absorbed dose of ionizing radiation. One rad is equal to the absorption of 100 ergs of radiation energy per gram of matter.

reactor, nuclear A device for supporting a self-sustained nuclear chain reaction under controlled conditions.

redox A general term describing oxidation-reduction reactions.

reduction The opposite of oxidation, decrease in positive oxidation number; gain in number of electrons by an atom or group of atoms.

rem Roentgen equivalent man: a unit of human biologic dose as a result of exposure to one or many types of ionizing radiation. It is equal to the absorbed dose in rads times the RBE (relative biological effectiveness) of the particular type of radiation being absorbed.

roentgen The quantity of x or gamma radiation such that the associated corpuscular emission per 0.001293 gram of air (i.e., 1 ml at 0° C and 760 mm) produces, in air, ions carrying 1 electrostatic unit of quantity of electricity of either sign.

saline Consisting of, or containing salt, NaCl. Physiologic saline is 0.9% NaCl by weight.

self-radiolysis A process in which a compound is damaged by radioactive decay products originating from an atom within the compound.

sequential imaging A series of closely timed images, usually performed on a rapidly changing distribution of radioactivity.

solute The constituent of a solution that is considered to be dissolved in the other, the solvent. The solvent is usually present in larger amount than the solute.

solvent The constituent of a solution that is present in larger amount, or constituent that is liquid in the pure state, in the case of solutions of solids or gases in liquids.

specific activity (1) The radioactivity or decay rate of a radioisotope per unit of mass of the element or compound (e.g., microcuries per millimole, disintegrations per second per milligram). (2) The relative activity per unit of mass (counts per minute per milligram).

static imaging One or a set of images, usually performed on a fixed or slowly changing distribution of radioactivity.

sterile Aseptic, not producing microorganisms; free from microorganisms.

stoichiometric Pertaining to weight relations in chemical reactions.

sublimation (chemical) Passing from the solid to the vapor state by heating.

sulfhydryl Sulfur-hydrogen group found in some proteins (—SH).

synthesis A process in which a new chemical compound is formed in a reaction.

target organ For imaging, the organ intended to receive the greatest concentration of a radioactive tracer; for dosimetry, the organ receiving the largest cumulated radioactivity or the organ for which the dose is being calculated.

thrombus A plug or clot in a blood vessel or in one of the cavities of the heart, formed by coagulation of the blood, and remaining at the point of its formation.

toxicity The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. It is expressed by a fraction indicating the ratio between the smallest amount that will cause an animal's death and the weight of that animal.

transition metals The metallic elements in the center of the periodic chart.

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