The Role of the Radiochemist in Nuclear Medicine

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The radiochemist plays a vital role in nuclear medicine. He can be useful as a professional scientist providing radiodiagnostic agents for routine clinical use, and if called upon he can run the in vitro and radioimmunoassay laboratory. As a teacher, he can make substantial contributions in training physicians and technologists in nuclear medicine, and as a researcher he can be valuable in developing new radiodiagnostic agents while working in close collaboration with physicians. At present, there is a shortage of these trained scientists, and colleges of health-related professions in major medical centers should institute programs to train these vitally needed professionals.

The growth of nuclear medicine has been spectacular over the last 10 years. There has been a tremendous increase in the number of nuclear medicine procedures, even in community hospitals. During 1965–70 the demand for radiodiagnostic agents showed a phenomenal increase of 20% to 25% per year.1 At present, the growth rate in medical centers averages about 15% per year. This growth can be attributed not only to greater awareness on the part of physicians concerning the availability of nuclear medicine consultation, but also to the introduction of improved instrumentation and a variety of new radiodiagnostic agents. The introduction of generator systems for on-site production of short-lived radionuclides (99mTc, 113mIn) in sterile injectable solutions resulted in widespread use of these radionuclides even in remote areas. In addition, a variety of simple kits became available for on-site preparation of different radiodiagnostic agents from these short-lived radionuclides.

These developments contributed to the continued growth of nuclear medicine. The success of nuclear medicine depends to a large extent upon the use of efficacious radionuclides and radiodiagnostic agents that possess specific localization in intended organs. The radionuclides and radiodiagnostic agents referred to above and in use today have been developed by scientists in both medical and basic sciences. The basic scientist referred to here may be classified as a radiochemist, even though the person could as well be a chemist, a radiobiologist, a pharmacist, or a physicist. Therefore, for the purpose of this discussion, the term radiochemist should not be taken literally, but rather as a designation of scientists who handle radiodiagnostic agents in nuclear medicine.

It might be appropriate here to clarify some of the terminology used in this discussion. The term radiopharmaceutical is often used to describe radionuclides and radionuclidic compounds, and it gives the impression these agents are pharmaceuticals. However, these compounds cannot be considered as pharmaceuticals, but only as radiotracers or radiodiagnostic agents. By definition,2 a pharmaceutical (a drug or medicine) is “a substance used in treating...

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disease, healing or relieving pain.” Certainly the radiodiagnostic agents used in nuclear medicine cannot be considered as pharmaceuticals. The quantities of chemicals (both radioactive and nonradioactive) used in these agents are so minuscule that they fall below the level of immunoresponsiveness even in sensitized individuals and therefore do not produce pharmacological effects in patients. The methods used to prepare these agents are more chemistry-oriented than those used in the traditional hospital pharmacy. The types of agents prepared by radiochemists are entirely of a different class than those ordinarily covered in traditional pharmacy training. Because of the minuscule amounts of chemicals involved, a whole new realm of solution tracer chemistry becomes very important with new and different methods of analysis and quantitation.

The only similarity between radiodiagnostic agents and pharmaceuticals is the necessity for quality-control standards for parenteral use (sterility and apyrogenicity). Therefore, these agents can appropriately be called radiodiagnostic agents rather than radiopharmaceuticals. An international panel convened by the International Atomic Energy Agency\(^2\) refused to define these agents as drugs (pharmaceuticals) and expressed concern that too rigid an application of unadapted controls devised for general drug administration might seriously limit the use of these agents. But the term radiopharmaceutical has come into common use to indicate the radiodiagnostic agents. Consequently, the radiochemistry laboratories are often called radiopharmaceutical laboratories or even radiopharmacies. The radiochemists are often mistakenly called radiopharmacists. But the IAEA international panel prefers the term radiopharmaceutical scientist to describe these scientists handling radiodiagnostic agents. In this discussion, the term radiodiagnostic agents will be used to describe radionuclidic compounds used in nuclear medicine.

**TYPES OF NUCLEAR MEDICINE FACILITIES**

According to a recent survey\(^4\) there are 7,061 accredited hospitals in the United States. In answer to a questionnaire to which 6,622 hospitals responded, only 2,550 (38.5%) are reported to have some nuclear medicine facility (January 1972 figures, the latest available). Included in this survey are 97 medical schools.\(^5\) Fifteen of them do not have any nuclear medicine. These nuclear medicine facilities are headed by a total of 5,061 physicians\(^6\) licensed to use radiodiagnostic agents for medical applications. These include 2,413 physicians in private practice. There are no statistics available on the number of radiochemists in these institutions.

The nuclear medicine facilities in these hospitals can be divided into three different types: (1) a small laboratory in a community hospital, often headed by a part-time nuclear medicine physician; (2) a large hospital laboratory with full nuclear medicine service with one or more full-time nuclear medicine physicians; and (3) a teaching hospital laboratory (medical center) associated with a medical school. At present, all the above hospitals have different types of facilities to prepare radiodiagnostic agents, which facilities are called radiochemistry laboratories. In general, a nuclear medicine laboratory may perform wholly or in part the following services: (1) organ imaging (this includes al-
most all major organs); (2) laboratory studies not involving imaging (iron kinetics, red-cell survival, Schilling tests, blood volume, thyroid uptake); (3) in vitro studies including radioimmunoassay.

ROLE OF RADIOCHEMISTS IN NUCLEAR MEDICINE

In a modern nuclear medicine laboratory, the radiochemist may be asked to perform the following tasks: (1) provide radiodiagnostic agents for routine clinical use on a daily basis, (2) run the in vitro analytical laboratory including radioimmunoassay, (3) participate along with the physician in teaching programs, (4) conduct and assist in basic and applied research programs involving radiodiagnostic agents. In the ensuing discussion, let us pragmatically explore how a radiochemist can successfully fulfill these obligations.

Record-keeping and Health Physics

The first three of the abovementioned functions of a nuclear medicine laboratory involve the use of radionuclides and radiodiagnostic agents, which may require the services of a radiochemist. Every laboratory is involved in purchase, stock, and disposal of long-lived radioactive agents in addition to short-lived nuclide generators, chemical kits, etc. Adequate records must be kept of these transactions, especially those records of use in patients. The legal responsibility for this rests with the physician. A radiochemist can help in these matters of record-keeping, developing purchase orders, receipt and checking of shipments of radioactive agents. A quality-control test on long-lived radioisotopes and their compounds may sometimes be necessary. This can be done by a radiochemist.

A properly trained radiochemist could assist the physician in health-physics aspects in a small hospital if a health physicist is not available. For small hospitals, it may not be financially feasible to employ a radiochemist, and in this case the nuclear medicine technologist can very well perform the above functions, since the work will involve only a small number of radioactive agents. The modern nuclear medicine technologist is well trained in these areas. In larger hospitals, a full-fledged physicist will be required to perform health-physics functions (radiological-equipment testing, etc.), with a full-time radiochemist to handle radiodiagnostic agents.

Laboratory Studies Not Involving Imaging

The nuclear medicine technologist is usually well trained in the clinical area of laboratory studies. Here, the radiochemist could assist in checking the radionuclidic purities and chemical integrity of agents used in these studies by performing analytical tests (paper and thin-layer chromatography, electrophoresis, multichannel radionuclide analysis, etc.) before clinical use. But this function is limited at the present time because of the excellent quality control of these long-lived radiodiagnostic agents by commercial suppliers.

In Vitro Studies and Radioimmunoassay

There is an increasing emphasis on the use of in vitro tests, especially radioimmunoassays, in nuclear medicine. According to commercial sources, the
growth rate in this area is much higher than that for organ-imaging radiodiagnostic agents. The types of in vitro studies performed in the nuclear medicine laboratory primarily use commercially available kits and standardized equipment. Here a thorough knowledge of analytical methods, nuclear instrumentation and basic immunochemistry is required to appreciate the various steps involved in performing the test. Quality control of the methodology is essential to perform these tests with equal confidence and reproducibility. A careful study of the pitfalls of each and every commercial kit is essential in the initial setup of the laboratory and for continued excellence in producing reliable results. The nuclear medicine physician is usually well trained to perform these tests and to supervise the laboratory. A well-trained radiochemist in this area can also offer professional service in maintaining the reliability of results, thus relieving the physician and allowing him to perform clinical tasks.

A well-trained radiochemist brings with him pertinent knowledge in chemistry, immunology, analytical testing, and handling of laboratory instrumentation, and he can perform troubleshooting tasks in this area. The major goal of this function of the nuclear medicine laboratory is reliable results. Since the physician sees only numbers at the conclusion of these in vitro tests, an extra effort in quality control in methodology is required. This extra effort can be provided by the radiochemist.

It must be pointed out here that there is a controversy over which laboratory should perform these tests. Is it the nuclear medicine laboratory or the clinical pathology laboratory? In most hospitals, the in vitro tests seem to be performed in nuclear medicine laboratories. No matter where these tests are performed, the radiochemist trained in this area brings with him unique qualifications for the job. As an example, even in a community hospital (if these tests are done in nuclear medicine), a radiochemist can prepare all the radiodiagnostic agents required for clinical use in the first hour of the morning and devote the remaining time to the in vitro analysis. This will not only reduce the cost of both operations but will also provide better service. However, the radiochemist should be well trained for both of these jobs.

Radiodiagnostic Agents for Routine Clinical Use

One of the primary functions of the radiochemist in the nuclear medicine laboratory is to provide radiodiagnostic agents for routine clinical use. This function differs from hospital to hospital depending on what services the individual laboratory provides. Based on this, the design and operation of the radiochemistry laboratory varies from institution to institution. Kawada et al. have described different designs for facilities providing radiodiagnostic agents. The types of radiodiagnostic agents a physician can use in clinical nuclear medicine are limited by the specifications of his federal and/or state license(s). This license is issued to the physician primarily on the basis of his education, training, and experience in nuclear medicine, in addition to the availability of trained scientists (radiochemists) and physical facilities of the nuclear medicine laboratory.

Let us discuss how a radiochemist can help these nuclear medicine labora-
tories in providing radiodiagnostic agents for routine clinical use. In a small community hospital, the physician generally will be limited to the use of only those radiodiagnostic agents approved by the FDA for routine clinical use. This limits the number of radionuclides he can use to less than 20 and the number of applications to about 50. These agents are usually subjected to good quality control by the manufacturer and do not need any special handling, except for ¹¹⁷mIn and ⁹⁹mTc generators and ¹³³Xe. Of late, the unit doses available for ¹³³Xe and excellent quality control of ⁹⁹mTc have reduced the chances of receiving poor radiodiagnostic agents.

Currently, the ⁹⁹mTc generators are individually tested for ⁹⁹Mo leak before shipment. If required, this test can be performed every day within a short time using standard nuclear medical instrumentation (dose calibrators or well counters or multichannel analyzer). Sterile kits are available to prepare radiodiagnostic agents from ⁹⁹mTc pertechnetate. The operation in most cases involves simple aseptic transfer of pertechnetate from one vial to the kit vial and calibrating the radiodiagnostic agent as to its radioactivity and affixing proper identifying label. To perform this simple task, a full-time radiochemist would be a big financial burden on the department, but if the same person could perform the in vitro laboratory tests, the cost could easily be justified. Well-trained nuclear medicine technologists can also perform this task admirably.

Because of the short half-life of ⁹⁹mTc and the fact that quality-assurance tests are rather time-consuming (especially sterility and pyrogenicity) these tests usually must be performed after the patient has been injected. Therefore, these tests are not very useful. However, it must be remembered that, except for those under investigation, these chemical kits are well tested prior to shipment by the manufacturer. Therefore, further testing will not help the patient. This applies only to FDA-approved radiodiagnostic-agent kits. A radiochemist, if available, can undertake this responsibility of providing routine radiodiagnostic agents in a community hospital in addition to running the in vitro (radioimmunoassay) laboratory and, once again, take this burden off the nuclear medicine physician who can perform other clinical tasks.

In a large hospital laboratory with full nuclear medicine service, the radiochemist can be very useful by providing the latest available radiodiagnostic agents (i.e., those under use by filing IND applications). There is usually a delay of at least 2 years before a radiodiagnostic agent is developed, tested for efficacy, and released for widespread use. The radiochemist could hasten the availability of these agents by preparing them in the radiochemistry laboratory, performing all the necessary tests of biological distribution, toxicity, and efficacy, to develop necessary data for filing the IND application and obtaining approval from local hospital committees, etc. Of course, he will be working with a competent, well-trained nuclear medicine physician.

A radiochemist can also perform a useful task by running a centralized radiochemistry laboratory from a single hospital, which can provide all the radiodiagnostic agents for other hospitals in the immediate vicinity. This work will involve the use of single or multiple radionuclide generators obtained from commercial sources along with various kits for daily preparation of radiodiagnostic agents. This includes using single or multiple kits in the prepa-
ration of a single radiodiagnostic agent, adding enough radioactivity, sub-dividing this into multidose vials, properly labeling the vials and delivering them to other laboratories. It may also include buying all the required long-lived radionuclides from commercial suppliers and redistributing these as required by other hospital nuclear medicine laboratories.

The major advantage of this facility is the savings in cost by sharing radioactive and nonradioactive materials and the bulk buying power that often results in reduction of the purchase price. To manage and run this type of facility, a well-trained radiochemist is essential, since it requires a thorough knowledge of chemistry and in vitro and in vivo stability of all the kit products. Record-keeping will have to be elaborate to keep track of which laboratory got what from which kit. Stiffer federal regulations may come into play in the operation of these laboratories. A qualified, well-trained radiochemist will be of immense help to the nuclear medicine physician in this type of laboratory.

The third type of radiochemistry laboratory, in a medical center, can provide all the required radiodiagnostic agents from locally made kits in addition to providing longer-lived radionuclidic compounds obtained from commercial suppliers. This laboratory will have adequate "manufacturing" facilities, quality-control equipment, animal-housing units, and facilities to study the in vivo stability and organ distribution of all the radiodiagnostic agents made from these locally made kits. Because of the scope of the operation, this laboratory will be strictly regulated by the federal and state agencies.

If materials are sold to other institutions, this laboratory may be considered a manufacturing facility and will be subject to regulations just like any other commercial manufacturer. The radiochemist will be responsible for all the operations of this laboratory and will be directly supervised by the physician who holds the legal responsibility for using in-house-made radiodiagnostic agents in patients.

A major advantage of this radiochemistry laboratory is also in savings in cost, but part of this savings may be offset by the expenditure involved in testing, quality control of these agents, and purchase of required specialized equipment. However, the real advantage is the availability of the most recently developed radiodiagnostic agents for local clinical use. Only a few institutions can afford to have this type of radiochemistry laboratory. Some institutional groups in one area may want to take advantage of this type of laboratory by sharing the total cost and responsibility for this operation and may benefit in sharing all radiodiagnostic agents prepared from locally manufactured kits. However, federal and state regulations may very strictly control this type of operation. In these situations, a qualified radiochemist is a very valuable professional.

Location of the Radiochemistry Laboratory

There have been several recent reports by pharmacists trained in radiochemistry\textsuperscript{7,10,11} suggesting that the preparation of radiodiagnostic agents be performed in the radiopharmacy, an extension of hospital pharmacy, and delivered to the nuclear medicine laboratory by individual prescription! One report\textsuperscript{10} even suggested that the radiopharmacist advise the physician (by consultation) as to which radiopharmaceutical to use for different studies. I
strongly disagree with these concepts of radiopharmacists. First of all, the nuclear medicine physician is a superbly trained specialist and he does not need advice from radiopharmacists as to which radiodiagnostic agent should be used for clinical studies.

Secondly, the preparation and use of radiodiagnostic agents is a major function of the nuclear medicine laboratory, and it does not belong anywhere else. The idea that analytical tests conducted in the pharmacy will alone sufficiently test the efficacy of radiodiagnostic agents is incorrect, and true efficacy can only be tested in patients after careful evaluation in experimental animals of proper choice. This type of research activity can only be conducted in close association with the nuclear medicine physician in the nuclear medicine research laboratory and not in the hospital pharmacy.

The separation of the radiochemistry laboratory from nuclear medicine and the institution of this function in the hospital pharmacy not only creates a bureaucracy with its own administration, space, separate instrumentation, and personnel, but also adds cost to the medical care. Ultimately, the patients will be paying an unnecessary additional cost. On the other hand, the radiochemistry laboratory that remains in nuclear medicine can share most of the facilities of already available instrumentation and will work in close cooperation with the nuclear medicine physician.

It is the prime responsibility of the nuclear medicine physician to see that his rights are protected and that the radiochemistry laboratory remains in the facilities of the departments of nuclear medicine under his supervision and not be in a remote corner in the hospital pharmacy.

Radiochemists in Research and Training

So far we have discussed only two of the four roles of the radiochemist in nuclear medicine. The others are in teaching and research, and they can be substantial if adequately utilized in nuclear medicine teaching institutions. The radiochemist brings with him an enormous store of information in addition to those available through the nuclear medicine physician. Therefore, in teaching and training of nuclear medicine physicians, he can be immensely helpful in providing basic information on radiodiagnostic agents, their chemistry, analytical problems, and quality control. He can teach basic sciences in these areas. In training nuclear medicine technologists, he can also be useful in laboratory training and course work dealing with radiodiagnostic agents.

Basic and applied research is another area in which the radiochemist can contribute to nuclear medicine. He can be involved in developing new radiodiagnostic agents in close working relationship with the nuclear medicine physician who knows the exact clinical problem that may be solved by a new radiodiagnostic agent. In fact, many agents used in nuclear medicine were developed by scientists of different disciplines working together with the nuclear medicine physician.

Education and Training of Radiochemists

In a recent article, Peng has eloquently discussed the need for individuals trained in handling radiodiagnostic agents in nuclear medicine. The importance
of nuclear medicine in a hospital has been well established with the creation of the American Board of Nuclear Medicine. As a result, there will be a substantial increase in the number of nuclear medicine laboratories. Many of these laboratories will need the expertise of trained radiochemists. However, these individuals are in short supply, and educational programs are being instituted in several universities. The first and foremost is the program conducted at the University of Southern California in Los Angeles. A large number of these educational programs are conducted in colleges of pharmacy in which only pharmacists are allowed to become these trained individuals. It is interesting to note the types of courses these people are taught. Any educator who is familiar with basic science curricula will recognize that a large number of graduates in the chemical and biological sciences with appropriate subspecialization have already taken these courses and experienced this training. It is reasonable to assume that if graduates in pharmacy can master these courses in chemical and biological sciences, graduates in these sciences similarly can master basic requirements in pharmaceutical sciences relevant to the field of radiodiagnostic agents; by this we mean courses in parenteral preparations, record-keeping, microbiology (sterility—pyrogen testing) and pharmacology. This cross-combination of graduates from both sciences definitely will strengthen the field. After all, the area of preparation and use of radiodiagnostic agents is a new field (a new profession), and if a new field in education or in a profession is becoming available it should be equally available to all qualified individuals. Thus training in “radiopharmacy” should not be restricted to graduates in pharmacy alone, but must be open to suitable graduates in chemical, physical, and biological sciences. These individuals each have deficiencies in the other areas and therefore should be exposed to and taught courses in the areas where they are deficient. To shut the door without reason is in violation of the basic principle of higher education in this country, which holds that every person should be allowed to become what he is capable of becoming.

Leaving politics to politicians, let us concentrate on the qualifications and training of the radiochemist. The radiochemist should have adequate training in the following areas: (1) basic nuclear physics, including nuclear medical instrumentation; (2) radiation biology; (3) tracer chemistry of inorganic elements; (4) health physics and radiation dosimetry; (5) pharmacology and pharmacokinetics as applied to radiodiagnostic agents; (6) parenteral preparations and their quality control; (7) preparation analysis and utilization of radiodiagnostic agents; (8) immunochemistry; (9) radioimmunoassay; (10) elements of nuclear medicine; (11) drug laws and governmental regulations; (12) research methods in nuclear medicine. Since we have defined an end product, who can become a radiochemist? Clearly, undergraduates or graduates in (1) radiochemistry (chemistry), (2) radiation biology (biology), (3) radiation physics (physics), and (4) pharmacy (pharmacology?) can become qualified in this field. It may not be necessary that graduates in the above fields take all the abovementioned courses. Some may be omitted if the individuals have adequate previous training. In addition to the course work, these individuals should undergo at least 6 months of practical training in a full-fledged nuclear medicine laboratory and actually be involved in all aspects of handling radiodiagnostic agents.
It seems that colleges of pharmacy have a monopoly in training the much-needed radiochemists, and it is about time that colleges of health-related professions in all the medical-school-oriented medical centers take a careful look at this area and take positive steps in providing training to qualified individuals to become radiochemists in nuclear medicine. This trained person is the radiochemist, who can become a responsible professional in handling radiodiagnostic agents and contribute to the well-being of the patients and ultimately to the continued effective growth of nuclear medicine.

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