medicine computers. These workstations are based on the UNIX, platform which implies a multi-tasking, multi-user system that is "open" in the sense that a source code can be readily transported between systems. Most manufacturers who have chosen this route of development have also adopted X-windows as the user interface.

Another parameter that will impact upon the use of computers is the greater realization that software can "break down" and faults can occur. The use of computers in medical systems is not without risk as has been tragically demonstrated by the overexposure of patients undergoing radiotherapy. These problems have not escaped the attention of the regulatory agencies, and, in the U.S., the Food and Drug Administration has established a program for the validation, acceptance, and quality asssurance of computer software used in medical systems. Presently, the degree of control over nuclear medicine software remains fairly loose on the basis that there is a human interface (the clinician) between the computer analysis and the diagnostic decision. This situation may change as greater emphasis is placed upon the use of knowledge-based systems (KBS) or artifical intelligence (AI) to provide a diagnostic optimization of the computer analysis.

In Europe, the COST-B2 project on Quality Assurance of Nuclear Medicine Software under the aegis of the Commission of European Communities is working towards similar objectives. In this case, however, it is the nuclear medicine community that is developing its own quality assurance program, working in cooperation with industry to ensure quality care.

In a review of this nature, it is natural to reflect upon the principal activity of nuclear medicine and to focus upon the scintillation camera/computer system. Computers have been applied to many other facets of nuclear medicine. For some time, PC-based systems have been available for tracking radiopharmaceuticals, and the records produced by such systems fulfill the Nuclear Regulatory Comission requirements. Systems for patient scheduling and accounting functions are much more common—particularly in larger departments attached to departments of radiology. Another development has been the use of widespread computer networks for electronic conferencing and electronic mail. Academic computers at thousands of universities are connected by a number of networks that collectively form The Matrix (*10,11*). One example of the value of these networks is to note that much of the data gathering and discussion related to the COST-B2 project mentioned above has been conducted via electronic mail. Collaboration of this magnitude would be considerably delayed if reliance had to be placed upon the normal postal services.

Nuclear medicine has witnessed some profound developments during the past 20 years. Its demise has been forecast several times as new and emerging technologies such as the computed tomography (CT) scanner and magnetic resonance imaging (MRI) gain acceptance. Despite such portents of gloom, nuclear medicine has managed, to not only survive, but to thrive. This resilience has been due in large part to the development of new and exciting radiopharmaceuticals and to the constant evolution of better instrumentation. Nuclear medicine remains a small part of the diagnostic process, but it continues to be an exciting field of endeavor with change and improvement being the one constant factor.

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A REVIEW OF RADIOPHARMACEUTICALS OVER THE PAST DECADE

OVER THE HILLS AND THROUGH THE WOODS??

"If I've told you once, then I must have told you a million times: Don't exaggerate the facts."

–Anonymous

Since Briner's descriptive use over two decades ago of the word radiopharmaceutical, several significant advances and developments in radiopharmaceuticals have occurred that account for revolutionary gains in the practice of nuclear medicine. While breakthroughs that have lead to new technetium-99m (^{99m}Tc) radiopharmaceuticals rank as the most immediately successful research, considerable gains are also being made in other areas, including radiolabeled antibodies and proteins, therapeutic radiopharmaceuticals, and

positron emission tomography (PET).

Advances in Technetium-99m Chemistry

Among all such development that have occurred to date, the most notable has probably been the advent of the $^{99}Mo/^{99m}Tc$ generator and its readily available supply of the nearly ideal radionuclide ^{99m}Tc. A primary disadvantage to the universal application of ^{99m}Tc, however, has been the limitations in the ^{99m}Tc labeling characteristics and the known number of tissue-specific molecules that can be labeled with this radionuclide. For some molecules, labeling is not yet feasible, or perhaps impossible, or undesirable as a result of the relatively short physical half-life of ^{99m}Tc (6.0 hr). In these situations, other radionuclides are necessarily employed.

Over the past decade, efforts in the area of technetium chemistry have been directed towards the identification of those molecules with tissue specificity and pathologic significance and those that may be suitably labeled with ^{99m}Tc. Most of these endeavors have centered upon basic research activities directed at greater understanding of the chemical nature of technetium. A lack of fundamental knowledge of technetium has plagued nuclear medicine from its inception since most of the previous information about technetium was based not upon direct observations, but on information regarding manganese and rhenium, other members of the same periodic group.

Hepatobilary Radiopharmaceuticals. In some cases the evidence is that serendipity played a significantly large role in radiopharmaceutical development. That gallium-67- (^{67}Ga) citrate was taken up by lymphoma was noted while performing bone imaging with this radiopharmaceutical in a patient with lymphoma. Similar situations have also occurred with ^{99m}Tc radiopharmaceuticals. Technetium-99m HIDA (lidofenin), the prototype of all subsequent ^{99m}Tc hepatobiliary radiopharmaceuticals, was initially investigated for its potential as an infarct-avid agent when this radiopharmaceutical was noted to localize in hepatocytes and undergo hepatobiliary transit. Further investigation revealed that the biodistribution of carbon-14-labeled HIDA was dramatically different from that of ^{99m}Tc-HIDA. Carbon-14 labeled preferentially underwent renal excretion rather than hepatobiliary excretion as was noted with ^{99m}Tc-HIDA. This finding suggested a greater role to ^{99m}Tc in the formation of ^{99m}Tc-HIDA. Later, x-ray diffraction studies confirmed the basis for this observation when it was revealed that ^{99m}Tc bound not one but two molecules of HIDA in the formation of a bis-compound. Researchers later found and reported for ^{99m}Tc-HIDA-analogues correlations between physicochemical parameters, structural effects, and in vivo biodistribution characteristics, including the fact that lipophilicity could be used to predict protein binding and in vivo distribution of these agents. Based upon these structural-distribution relationships, new HIDA-type analogues have followed that have improved hepatocellular specificty and more desirable hepatocellular transit in the face of elevated serum bilirubin levels.

Technetium-99m Myocardial Perfusion Agents. The production of thallium-201 (^{201}Tl) during the early 1970s represented a significant development in quest to perform noninvasive myocardial perfusion imaging. Difficulties associated with the less than ideal nuclear imaging properties of ^{201}Tl, however, and the logistics imposed upon users by the need for overnight air freight deliveries have favored research towards a ^{99m}Tc-labeled radiopharmaceutical with similar biodistribution properties and/or suitable clinical usefulness. While such a development has long been a goal of researchers in radiopharmaceutical chemistry, only recently have ^{99m}Tc-labeled compounds been identified that distribute within the myocardium in relation to blood flow. Technetium-99m-DMPE (dimethylphosphinoethane), the first of these series, demonstrated high quality images of myocardial perfusion in dogs but failed in clincal trails to yield similar results. Subsequently, two ^{99m}Tc radiopharmaceuticals, [^{99m}Tc]sestamibi (Cardiolite, Dupont Inc., N. Billerica, MA) and [^{99m}Tc]teboroxime (Cardiotec, E.R. Squibb and Sons, Princeton, NJ) have been developed that yield successful images of myocardial perfusion.

Technetium-99m-cardiolite is a member of the isonitrile class of radiopharmaceuticals that have demonstrated good myocardial uptake comparable to that of ^{201}Tl. Technetium-99m-cardiotec is a boronic acid adduct of technetium oxime (also known as a BATO derivative). The BATO agents are neutral, seven-coordinate technetium complexes that have shown rapid myocardial uptake and clearance and relatively low uptake in the liver and lungs.

While these agents represent significant research breakthroughs in the search for a ^{99m}Tc-labeled replacement for ^{201}Tl, very real differences exist between these agents and the one they are intended to replace. For example, neither ^{99m}Tc radiopharmaceutical achieves a myocardial extraction efficiency as high as that of ^{201}Tl. Localization of the ^{99m}Tc radiopharmaceuticals cannot be explained by the sodium-potassium ATAP-ase exchange mechanism as occurs with ^{201}Tl and neither [^{99m}Tc]sestamibi or ^{99m}Tc-cardiotec undergoes myocardial redistribution (necessitating a second injection of either agent in order to obtain diagnostic information during both rest and stress phases). Additionally, significant differences exist in the myocardial "washout" rates of these two radiopharmaceuticals. Technetium-99m isonitriles (including ^{99m}Tc-cardiolite) tend to have lengthy myocardial retention requiring that same-day stress and rest imaging utilize a much larger second dose of the radiopharmaceutical in order to distinguish infarction from stress-induced ischemia. On the other hand, ^{99m}Tc-cardiotec clears rapidly from the myocardium thus requiring that imaging be initiated as early as 2–3 min after injection and completed within

15–20 min.

A general concern that has been mentioned in association with "timeliness" of imaging of these agents is whether the initial distribution of these agents into other organs and the subsequent release into blood may permit uptake by areas previously noted as ischemic during stress at the time of imaging.

The likelihood of either of these radiopharmaceuticals entirely replacing ^{201}Tl is a subject of much conjecture. Regardless, it is clear that a ^{99m}Tc radiopharmaceutical is considerably more convenient than ^{201}Tl and presents with superior imaging properties.

Renal Imaging. For years, nuclear medicine has been a stanchion of renal diagnostics by offering a variety of procedures most of which involve the use of ^{99m}Tc radiopharmaceuticals. Studies of renal plasma flow, however, have been necessarily performed with radioiodinated orthoiodohippuric acid (OIHA), a radiopharmaceutical that has been around for the past 30 years. Only recently has a suitable ^{99m}Tc analogue been developed which has the characteristics of a renal plasma flow agent.

Technetium-99m-mertiatide (TechneScan MAG3, Mallinckrodt Medical, St. Louis, MO) was developed as a result of earlier efforts to develop chelating agents for technetium based upon amide nitrogen and thiolate sulfur donor groups. Early attempts aimed at demonstrating a ^{99m}Tc agent with renal extraction and excretion properties comparable to radioiodinated OIHA were largely unsuccessful (renal elimination rates were less than OIHA, or multiple isomeric complexes were formed during radiolabeling that required impractical separation via HPLC techniques). The nonisomeric triamide mercaptide lignad, mercaptoacetyltriglycide (MAG3, or mertiatide) has shown renal clearance rates that strongly correlate with effective renal plasma flow and with a usefulness as a direct measure of renal function. While ^{99m}Tc-mertiatide is (at the time of this writing) classified as an investigational agent, most clinical studies have shown the strong correlation between this agent and radioiodinated OIHA clearance permits the substitution of this agent for OIHA as an estimator of effective renal plasma flow.

Brain Imaging. Nuclear medicine initially built its name around conventional brain imaging with the use of water soluble radiopharmaceuticals that cross only damaged areas of the blood brain barrier (BBB). In the area of diagnostic brain imaging, however, the utility of nuclear medicine has diminished substantially with the advent of computerized tomography (CT) and magnetic resonance imaging (MRI). Within the past few years, however, SPECT imaging and the development of two lipophilic radiopharmaceuticals, iodine-123-p-isopropylamphetamine (Spectamine, Medi+Physics, Inc., Paramus, NJ) and ^{99m}Tc-exametazime (Ceretec, Amersham, Inc., Arlington Heights, IL) have revolutionized the concept of nuclear medicine brain imaging. These radiopharmaceuticals cross the intact BBB by virtue of their lipophilic character and distribute in brain tissues in proportion to blood flow. In addition to ^{99m}Tc-exametazime, other new ^{99m}Tc radiopharmaceuticals are in various phases of development and have shown effectiveness in brain imaging, including ^{99m}Tc-ECD (L,L-ethyl cysteinate dimer, also known as Neurolite, Dupont, N. Billerica, MA) and ^{99m}Tc-DADT (diamine dithiol).

Radiolabeled Antibodies and Proteins

During the past several years, the potential benefits of monoclonal antibody technology to medicine has been consistently repeated without widespread evidence of impending success. The realization of the potential of radiolabeled monoclonal antibodies has been difficult to achieve. At this time, no radiolabeled antibody has been approved by the Food and Drug Administration (FDA). While some may be close to approval, and many are on the horizon, the role of radiolabeled antibodies in the practice of nuclear medicine is still very uncertain.

At this point, however, certain technologic benefits have been realized in association with monoclonal antibody research. The area of bifunctional chelating agents, for example, has been and continues to result in better "linkers" to attach radionuclides to biologic molecules such as proteins and peptides. With improved linkers comes the promise of more stable radiopharmaceuticals and the ability to attach a wider variety of diagnostic as well as therapeutic radionuclides to biologically active molecules.

Therapeutic Radiopharmaceuticals

With the notable exception of iodine-131- (^{131}I) sodium iodide, nuclear medicine has essentially abandoned any widespread use of all other therapeutic radionuclides, particularly those that are administered parenterally. This abandonment has not been due to lack of clinical need or interest, but rather due to the lack of available agents which can deliver lethal radiation doses to tumors while sparing normal radiosensitive tissues.

It is possible that this scenario may be changing with the recent development of several new radiopharmaceuticals that are intended to deliver therapeutic doses of radiation and which may be given parenterally.

These radiopharmaceuticals, including strontium-89-chloride, rhenium-186-(Sn)-HEDP, samarium-153, and [^{131}I]MIBG (an older diagnostic radiopharmaceutical that is being utilized in increasingly larger amounts for therapy), are in various phases of clinical investigation and appear to hold significant promise for therapy in nuclear medicine.

Positron Emission Tomography (PET)

One of the "buzz" words of the nineties appears to be *clinical PET.* Whereas this imaging modality has been previously restricted to major research institutions, proponents of the

speciality and equipment manufacturers hope for PET on every street corner, or at least on every other corner.

The use of these ultra-short radionuclides bring a new complexity to the compounding and dispensing of radiopharmaceuticals. In fact, the current posture of the FDA is that the PET activities do not constitute compounding and dispensing but rather are within the realm of drug manufacturing. Such implications of this regulatory position upon the traditional practices of nuclear medicine and nuclear pharmacy are enormous and deserve close monitoring. While such a position is subject to change, the regulatory manner and method under which PET facilities currently operate lack uniformity. The radiopharmaceutical issues surrounding the use of PET agents will be a major challenge to radiochemists, nuclear pharamcists, and nuclear medicine technologists for years to come. In this regard, the role of the automated synthesis modules that are used to prepare radiochemicals that are later determined of pharmaceutical quality is a central issue to the practice of clinical PET.

The Future

Radiopharmaceutical development has progressed from a random walk through shelves of reagents to an organized plan of drug design based upon demonstrated structural-activity relationships. Additionally, biotechnology has opened up vast new areas of potentially advantageous materials which lend themselves to possible radiodiagnostic and radiotherapeutic applications. The last decade has witnessed many dramatic changes in radiopharmaceutical chemistry that have impacted favorably the ability of nuclear medicine to perform new and clinically important noninvasive procedures. These procedures and their availability will surely demonstrate an even brighter future for nuclear medicine.

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