Variables in Radiotracer Kinetics and Biodistributions

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"If the Lord Almighty had consulted me before embarking on the creation I would have recommended something simpler."
Alfonso X of Castile
Medieval Patron of Astronomy

It is possible, several hundred years later, to have some sympathy with Alfonso X when he protested the complexity of the world, even as it was perceived in the Middle Ages.

If nuclear medicine practice was simple, in any given patient, the injection of a radiotracer might result in scintigraphic images that are either normal or abnormal. In the latter case disease will be present. The reality is, however, more complex and challenging. Since the tracer method reflects subtle alterations in physiology, scintigraphs may reveal not only disease but treatments, drug toxicity and medical interventions. In addition, factors in the habits and lifestyle of patients will also result in changes that may be recognized scintigraphically.

In this editorial, we wish to describe some of the types of changes in radiopharmaceutical biodistributions which are due to influences other than the direct effects of disease.

INTERVENTIONS IN NUCLEAR MEDICINE

It is often possible to increase the sensitivity of nuclear medicine techniques by the use of an intervention. Examples are administration of a drug at the time of the scan or a request for the patient to follow some particular protocol for exercise or diet. One such intervention is the use of the angiotensin converting enzyme-inhibitor captopril to increase the sensitivity of renography when used to diagnose a renal artery stenosis as a cause of high blood pressure. The subject of interventional techniques in nuclear medicine is a large one and has been addressed in a monograph (*1*). They will not be discussed to any great extent here.

IATROGENIC CHANGES IN RADIOTRACER BIODISTRIBUTIONS

Changes in scintigraphic images may be the result of medications as well as medical and surgical procedures. Like other effects that result from treatments these are called "iatrogenic," the word being derived from the root *iatros* which is Greek for physician.

Observation of several of these effects led to a review by our group and others (*2*). The number of such changes resulted in further reviews (*3–4*) but they are made rapidly obsolete by yet more reports. These iatrogenic changes in tracer biodistributions can be classified by a modification of the scheme used by Avery (*5*). He used it in describing the interactions of nonradioactive drugs. This classification is as follows:

Pharmacologic

Certain drugs may be given for a reason that coincidentally also directly interferes with the use of a radiopharmaceutical. For example, etidronate disodium is administered to patients with osteoporosis or Paget's disease of the bone. This is done to inhibit bone turnover, but, presumably by competition, this drug reduces the uptake of technetium-99m- (^{99m}Tc) phosphates. The result is a poor quality bone scan with reduced activity in bone and high blood concentrations of the tracer (*6*). Such effects of drugs that are the result of the intended action in the body and are, therefore, properly called pharmacological.

Pharmaceutical

Other drugs may be administered and prove to have physiochemic properties which influence the biodistribution of a radiotracer. For example, the administration of compounds containing iron by injection for the treatment of anemia will also result in high blood concentrations and poor bony uptake of ^{99m}Tc-phosphates when injected (Fig. 1). This effect, as might be expected, is more marked the closer these events are related in time. The exact mechanism is uncertain but it is believed that transchelation occurs whereby the radiolabel is detached from the phosphate and becomes bound to the iron containing compound (*7*) (Fig. 1).

Not all such effects may depend strictly upon a drug which has been given to a patient as a deliberate strategy. It has been reported that the aluminum leached from the needles used to transfer indium-111- (^{111}In) tropolone when used for cell

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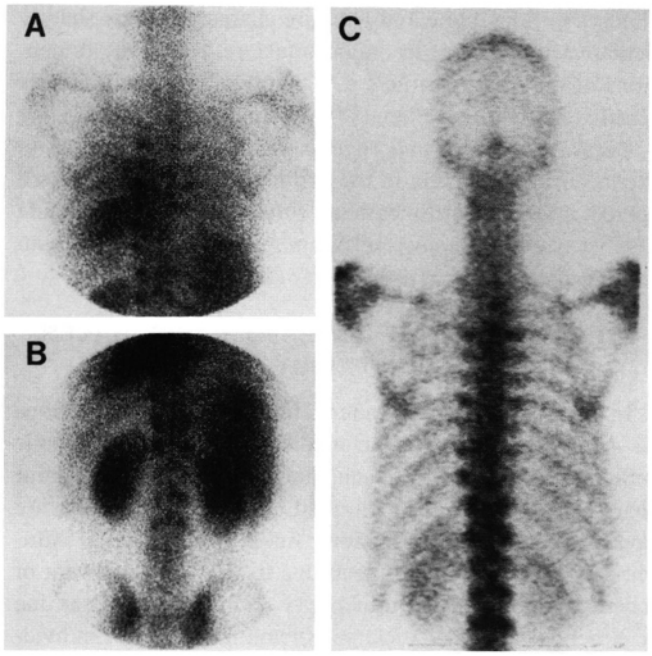

FIG. 1. (A-B) Posterior images of the dorsal and lumbar spine made 2.5 hr after injecting ^{99m}Tc-methylene diphosphate. The patient had been given intramuscular iron the day before to treat anemia. The result is poor bone uptake of the radiotracer with abnormally great concentrations of radiotracer in blood (chiefly heart, liver and spleen). (C) The same patient as Figure 1A-B. Normal scan made the same time after injecting the radiotracer 5 days later.

labeling was sufficient to cause precipitates which were trapped in the lung when the preparation was injected (*8,9*).

Toxicologic

It is well known that many medications result in toxic effects upon tissues and organs. For some of them this toxicity is the limiting factor in their administration. The reasons for the toxicity are not always understood. However, such toxic effects are often revealed during radionuclide scintigraphy (Fig. 2). An example is the pulmonary inflammation caused by drugs such as bleomycin and nitrofurantoin, demonstrating abnormal, increased concentration of gallium-67- (^{67}Ga) citrate in the affected areas. Histologically, this inflammation is often little different from the inflammatory diseases of lung which we often asses with ^{67}Ga-citrate. It is not surprising, therefore, to find that lung toxicity caused by drugs (Table 1) (*2,10*) results in this increased uptake of gallium (Fig. 3).

Some more recent reports have indicated other examples of ^{67}Ga scintigraphy being modified by drug toxicity. One account in a patient with chloroquine toxicity reported the localization of radiogallium in the heart and kidneys which are precisely the organs most affected by chloroquine (*11*). In another patient with aluminum toxicity, treated with deferoxamine, ^{67}Ga scintigraphy was remarkable in revealing what appear to be a high blood concentration of the radiotracer with virtually no organ localization (*12*). Aluminum toxicity, may occur from ingestion of large amounts of antacid containing aluminum hydroxide (the mild-alkali syndrome). It also occurs in patients with renal failure treated by dialysis.

TABLE 1. Drugs Which May Cause Pulmonary Interstitial Fibrosis (*10*)

Bleomycin
Busulphan
Carmustine (BCNU)
Chlorambucil
Cyclophosphamide
Cytarabine
Lomustine (CCNU)
Melphalan
Methotrexate
Mitomycin
Nitrofurantoin
Procarbazine

The pulmonary diseases associated with these drugs has not, in every case, been reported to be associated with increased uptake of ^{67}Ga. However, with the exception of carmustine, the clinical and histological features associated with each are so similar that the drugs can all be realistically considered to be at least potential causes of radiogallium localization.

Carmustine is unusual in that the pulmonary fibrosis may take years to develop after treatment, and affects the upper rather than lower lungs.

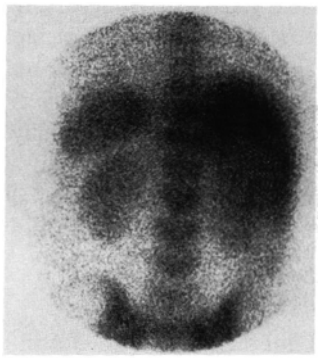

FIG. 2. Posterior image from a ^{67}Ga-citrate scan obtained 48 hr after injection of the radiotracer. The enhanced renal accumulation is due to cyclosporine, a nephrotoxic drug which had been used to treat the patient.

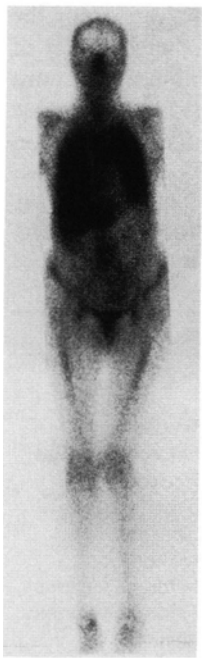

FIG. 3. Anterior image from a ^{67}Ga-citrate scan obtained 48 hr after injection of the radiotracer. The patient had been treated with methotrexate which caused pulmonary toxicity resulting in abnormal localization of the radiotracer.

Hyperaluminemia results in bone scans in which the bone uptake is greatly reduced, apparently because the aluminum blocks the deposition of radiotracer at sites of osteoblastic activity (*13*).

Aluminum and its implications for nuclear medicine might almost be the subject of a separate essay. It is well known that breakthrough of aluminum from $^{99}Mo/^{99m}Tc$ generators causes flocculation of ^{99m}Tc-labeled radiocolloids and their consequent localization in lung (*2,13*).

Perhaps one of the underused applications of radionuclide methods is to study drug toxicity and the resultant modification of treatment. One such widely used method is the application of radionuclide angiocardiography to detected myocardial toxicity from drugs such as adriamycin (*15*).

Pharmacokinetic

Some drugs, by their absorption, distribution, metabolism or excretion have an impact on methods used in nuclear medicine in altering the kinetics of radiotracers. An obvious example is the effect of iodides (such as potassium iodide, or in kelp) on the radioiodines used to diagnose thyroid disease, either qualitatively or quantitatively.

There is a formidable list of drugs that will reduce the uptake of radiotracers by the thyroid gland (*16*). Indeed, any specific uptake mechanism, and particularly those that are receptor-determined, will be prone to kinetic alterations from administered drugs which compete for binding sites. This is borne out by the formidable list of drugs which either actually or potentially alter the uptake of radiodinated metaiodobenzyl-quanidine (MIBG) either in the adrenals, in neural crest-derived tumors or in other β-adrenergic receptor sites (*17*) (Table 2).

Physical

This group of interactions was not included in the classification of Avery (*5*). However, it is necessary to include it here as a range of physical factors are found to influence the distribution of radiopharmaceuticals. These vary from the irradiation of patients, to surgery and to altered routes of injection. Even relatively trivial insults such as local injections may cause scintigraphic abnormalities (*18,19*). Most of these effects are readily recognizable. In particular, radiation changes in lung, bone and liver are characterized by sharply demarcated decreases in organ uptake reflecting the dimensions of the treatment field (*2*). Scintigraphy is particularly sensitive to radiation changes in the lungs (*20*).

Occasionally cause and effect is a little more obscure as in the localization of ^{67}Ga in the abdomen as a result of starch spilled into the peritoneum at surgery (*22*). Lastly, quite distinct syndromes may result from medical interventions, an example being dialysis arthropathy (*23*).

TABLE 2. Some Drugs Which Interfere (or Potentially Interfere) with Adrenal Uptake of Labeled MIBG

Drug	Probable mechanism
Antipsychotics (phenothiazines, thioxamthines, butyrophenones)	Uptake-1 inhibition
Adrenergic neurone blockers (guanethidine)	Transport competition, Depletion of storage vesicles
Calcium channel blockers	? (also block release)
Cocaine	Uptake-inhibition
Labetalol	Uptake-1 inhibition
Reserpine	Uptake-1 inhibition, Depletion of storage vesicles
Sympathomimetics	Depletion of storage vesicles
Tricyclic antidepressants	Uptake-1 inhibition

OTHER CAUSES OF ALTERED RADIOTRACER BIODISTRIBUTIONS

In the original reports of altered radiotracer biodistributions (*2-4*), the emphasis was on medication or other iatrogenic influences as the cause of such alterations. It is now apparent that such a view was too limited. Increasingly, reports are appearing of altered scintigraphic findings as a result of influences which we will describe as due to "lifestyle" for want of a better name. Lifestyle influences we will classify here as due to either occupational, dietary, recreational factors or individual habits. This classification is likely to be improved.

Occupational

Considering the range of potentially hazardous materials and environments present in many occupations it is surprising that there are few descriptions of these factors altering scintigraphic findings. Seaton et al. found lung perfusion defects at sites of pneumoconiosis evident on the chest radiographs of coal miners (*24*). More recent evidence suggests that atmospheric pollutants may influence pulmonary absorption of ^{99m}Tc-DTPA (*25*).

Lead poisoning causes an inhomogeneous distribution of radiocolloid in the liver in common with a number of factors (*26*), particularly some medications.

Otherwise occupational disorders noted scintigraphically have largely been confined to traumatic effects such as stress fractures in ballet dancers (*27*) and the uptake of ^{99m}Tc-phosphates in muscle damaged by electrical burns (*28*). It may be that a range of more subtle findings remain to be described.

Dietary

The impact of food intake on tracer distributions may be either specific or nonspecific. In a nonspecific way ingestion of food increases the splanchnic circulation as might be anticipated, and this effect has been observed scintigraphically (*29*). A particular result of this nonspecific effect is the impairment of ^{201}Tl redistribution in patients with myocardial ischemia who have a meal, as described by Angello et al. (*30*). Angello and his colleagues have also described a specific effect of ribose on ^{201}Tl redistribution (*31*). In rats, a dietary magnesium deficiency (which also does occur in man) has been shown to influence ^{201}Tl kinetics and distribution (*32*). Lastly, ^{67}Ga distributions have been found to be altered by dietary factors in experimental animals (*33*) although the changes would be unlikely to be evident on images alone.

It is possible that some of these effects may be indirect. A recent disturbing case report indicates that caffeine ingestion

may modify a patient's response to dipyridamole (*34*). Although this is an isolated report it is known that the methyl xanthines (of which caffeine is an example) act as adenosine inhibitors. Since the action of dipyridamole is thought to be mediated by adenosine it is likely that this report will be substantiated.

Recreational

As the range and extent of our recreational pursuits increases there is ample evidence that we may see the consequences in our patients. Indeed the many variations of bony trauma suffered by joggers and other athletes has given rise to the subspecialty of nuclear sports-medicine (*35*).

A more disturbing report is that of multiple defects in the distribution of cerebral blood flow in divers, as examined with ^{99m}Tc-hexamethylene propylene amine oxime (HMPAO) (*36–37*). Other reports have documented effects which are perhaps more trivial but potentially important in interpreting images. One example is altered uptake of radiotracer in the shoulder, demonstrated on a bone scan as a result of recoil from a weapon used in hunting (*38*).

Personal Habits

It is now well known that smoking influences the absorption of ^{99m}Tc-chelates, administered by aerosol, from lungs (*39*). It has also been described as causing an increase in the pulmonary localization of ^{201}Tl. Nicotine, like several other drugs, also prolongs gastric emptying (*40*).

Cocaine causes changes in both the brain (*41*) and myocardium (*42*). Mena et al. have noted an occasional reduction in cerebral blood flow measured with xenon-133 as well as multiple focal lesions on imaging with ^{99m}Tc-HMPAO following cocaine abuse (*41*).

The role of alcohol in causing hepatic cirrhosis is too well known to require documentation here. There seems little doubt that for as long as people have recourse to such drugs they may cause not only obvious disease but also subtle changes in physiology.

THEORETICAL ASPECTS

This is not the place to consider in detail theoretical considerations which relate to the changes we have indicated. This subject has been addressed, although necessarily not exhaustively, by Hodges (*43*) with respect to drug-induced alterations in tracer distributions. He has pointed out that much of our understanding remains incomplete. Certainly structure-activity relationships which relate chemical structure to biological activity provide a basis for understanding. Equally they suggest that as conventional nuclear medicine follows the example of positron tomography in increasingly evaluating cell-receptor sites then this will be a context in which the effects of medication will be important, as a variety of psychotropic drugs, for example, cause altered cell membrane transport or receptor blockade, or both. No doubt, as our understanding of the mechanism of localization of radiopharmaceuticals increases, then we will be better able to understand and anticipate their altered biodistributions.

PRACTICAL ASPECTS

When faced with unusual scintigraphic findings it may be difficult to unravel cause and effect. Both libraries and books have indexes which tend to be oriented towards diseases, or at best radiopharmaceuticals. We use the strategy of keeping a reprint of a catalogue of effects on file (*4*) and we update ours as each new report appears. One of us has been able to describe several drug-radiopharmaceutical interactions by keeping an index of unusual appearances and then simply seeking a common factor when several similar findings are recorded.

Equally we should be alert to the creative aspects of this topic. The recognition of the cell-labeling by reduced ^{99m}Tc, when pertechnetate was injected shortly after administration of a radiopharmaceutical containing stannous ions, led to a number of new clinical techniques.

SUMMARY

In this editorial we have tried to provide a perspective concerning the types of altered biodistributions that may be encountered in clinical practice where the cause has more to do with the patient and his or her treatment rather than disease per se. No attempt has been made to be exhaustive. Indeed one of the monographs which document conventional drug-drug interactions now runs to over 500 pages (*44*) and a similarly sized nuclear medicine analysis may be waiting to be written in the near future.

With the increasing sophistication of our methods in nuclear medicine, there is a matching need for us to understand what we mean by "normal" and what may be merely change induced by factors other than disease. Indeed, we believe it can be stated as an axiom that as clinical nuclear medicine is used to examine and measure increasingly sophisticated physiological processes there will be a proportional increase in the rigor with which we will need to control for confounding variables.

The size and complexity of this subject is formidable. Its scale is now beyond the skill, aptitude or wish of most of us to memorize. This fact is almost a prescription for some computed registry. Also the data base varies greatly from the anecdotal to the carefully documented report supported by bench research. Perhaps one immediate requirement is a clearing house (perhaps supported by The Society of Nuclear Medicine) that will allow each of us to have access to or keep abreast of the factors we have considered here. We recognize that the changes we describe range from important to trivial. Nevertheless, bizarre or unexpected findings, when examining patients, will often have their explanation in the kinds of changes we have described and must not be attributed to disease.

To return to Alfonso X, there is little doubt, despite such protests, that our lives will continue to increase in complexity. We in nuclear medicine will probe bodily functions with methods of increasing power and specificity. Technologists can share in the response to these increased opportunities. In their often more immediate contact with the patient they may

alert physicians to those medications or "lifestyle" variables that influence or potentially influence diagnostic methods. These greater responsibilities are a measure of the greater opportunities we will have in the diagnosis and treatment of disease. The increasing power of the tracer method implies a proportional increase in our need to understand the full range of influences upon tracer kinetics and distributions.

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