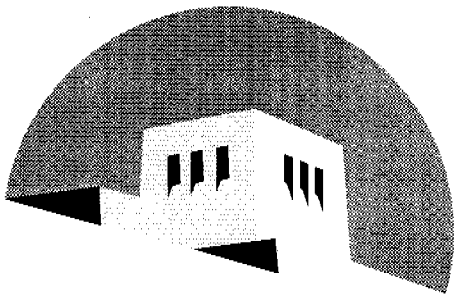

The University of New Mexico

THE UNIVERSITY OF NEW MEXICO
COLLEGE OF PHARMACY
ALBUQUERQUE, NEW MEXICO

Correspondence Continuing Education Courses for Nuclear Pharmacists and Nuclear Medicine Professionals

VOLUME III, NUMBER 4

Pulmonary Localization of Non-Solid-Particle Radiopharmaceuticals: Clinical, Anatomic, Functional, and Therapeutic Implications

By:

John J. Coupal, Ph.D., BCNP

Co-sponsored by: mpi pharmacy services inc
an Amersham company

The University of New Mexico College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. Program No. 180-039-93-006. 2.5 Contact Hours or .25 CEU's

Pulmonary Localization of Non-Solid-Particle Radiopharmaceuticals: Clinical, Anatomic, Functional, and Therapeutic Implications

By:

John J. Coupal, Ph.D., BCNP

Editor

and

Director of Pharmacy Continuing Education

William B. Hladik III, M.S., R.Ph.
College of Pharmacy
University of New Mexico

Associate Editor

and

Production Specialist

Sharon I. Ramirez, Staff Assistant
College of Pharmacy
University of New Mexico

PULMONARY LOCALIZATION OF NON-SOLID-PARTICLE RADIOPHARMACEUTICALS: CLINICAL ANATOMIC, FUNCTIONAL, AND THERAPEUTIC IMPLICATIONS

STATEMENT OF OBJECTIVES

The goal of this correspondence lesson is to inform the reader of several blood-soluble radiopharmaceuticals and their potential applications for diagnosis and treatment of human lung disease. To be discussed are structural aspects of the lung microcirculation, functional roles of the pulmonary endothelium, and major differences in kinetics of retention and washout of endogenous and exogenous soluble compounds after reaching the lungs via the systemic circulation. Unlabeled and various radiolabeled compounds localizing in lung will be compared in terms of their subcellular, tissue, and whole-organ uptake and subsequent kinetics in laboratory animals and in humans with and without disease. Also discussed will be the subtle effects of tobacco smoking, an injurious blood-borne chemical, and external irradiation on the lungs that can be objectively identified and measured, not by radiography, but by scintigraphy. Finally, the optimistic potential for nuclear medicine to out-perform X-ray, CT, MRI, surgery, and "conventional" medications, in diagnosing and treating structural and/or functional diseases of the lungs will be reviewed.

Upon successful completion of this material, the reader should be able to:

1. Describe the basic structure of the lung capillary vessel.

2. Distinguish between exogenous and endogenous organic and inorganic compounds and elements localized in lung from the circulation.

3. Explain the currently-uncertain factors resulting in uptake, retention, and washout of organic compounds (and their metabolites) from lung tissue.

4. Identify several non-malignant and malignant diseases of lung, along with appropriate organic radiopharmaceuticals having potential for diagnosing and/or treating such diseases.

COURSE OUTLINE

I. INTRODUCTION

II. THE LUNG MICROCIRCULATION

III. A COMMON AMINE INHALED INTO THE LUNG

IV. CIRCULATION DELIVERY OF BIOGENIC AND EXOGENOUS AMINES TO THE LUNG

V. RADIOLABELED EXOGENOUS AMINES

- A. Diamine
- B. Monoamine

VI. RADIOLABELED EXOGENOUS AMIDE

- A. Benzamide Derivatives

VII. TECHNETIUM-99m CHELATES AND THE LUNG

- A. A Diamine Bisoxime
- B. Diamine Dithiol Ligands
- C. Isonitriles

VIII. INDIUM-111 LABELED PEPTIDE

IX. NON-MALIGNANT LUNG DISEASE

- A. Respiratory Distress Syndrome
- B. Emphysema

X. MALIGNANT LUNG DISEASE

XI. CONCLUSIONS

PULMONARY LOCALIZATION Of NON-SOLID-PARTICLE RADIOPHARMACEUTICALS: CLINICAL ANATOMIC, FUNCTIONAL, AND THERAPEUTIC IMPLICATIONS

By:

John J. Coupal, Ph.D., BCNP
Nuclear Pharmacist
Veterans Affairs Medical Center
Nuclear Medicine Service
and
Associate Professor (Voluntary)
Department of Diagnostic Radiology
Division of Nuclear Medicine
University of Kentucky College of Medicine
Lexington, Kentucky

INTRODUCTION

To date, nuclear medicine has had a limited (although sometimes crucial) role in the diagnosis of selected diseases of the lung (e.g., in pulmonary embolism).

Ironically, due to the constantly improving characteristics of the newer brain imaging radiopharmaceuticals, those agents have shown potential applications in lung imaging. The similarity of physicochemical characteristics among these radiopharmaceuticals coupled with similarities between the blood brain barrier (BBB) and the lung endothelium appear to play a major role in such potential.

We have come far since the days when nuclear medicine could largely demonstrate only lung ventilation (by inhaled inert gases or aerosols) or perfusion (temporary physical blockage of some smaller lung blood vessels). Since our lungs are constantly exposed to both the ambient gaseous atmosphere as well as our systemic blood circulation, they are susceptible to assault from external as well as internal forces. Many newer blood-soluble radiopharmaceuticals appear capable of noninvasively demonstrating even subtle structural and functional features of the lungs and subsequent changes thereto; those features and later changes can range all the way from the harmless to the deadly.

THE LUNG MICROCIRCULATION

The capillary blood vessel of the lung appears to play a major role in concentration of certain soluble radiopharmaceuticals from the blood. The capillary is a cylindrical tube (about 8 μm in diameter, the size of an erythrocyte) lined by endothelial cells forming the semi-permeable endothelium whose main function is transvascular exchange (1). Surrounding the endothelial cells is a continuous basal lamina, a moderately electron-dense band, 50 to 70 nm thick, following the contour of the bases of the endothelial cells. The capillaries of the lung are characterized as "continuous" as are those of skeletal, smooth, and cardiac muscle along with those of the central nervous system. Capillaries in other tissues and organs are characterized as either "fenestrated" or "discontinuous." The cytoplasm of the endothelial cell has relatively few mitochondria adjacent to the nucleus, a sparse endoplasmic reticulum with ribonucleoprotein granules, a Golgi complex close to the nucleus, microtubules, lysosomes, vesicles, and three distinct types of filaments. The greatest mass of cytoplasm abuts the nucleus. Both acid and alkaline phosphatase activities are found in the cytoplasmic vesicles.

A COMMON AMINE INHALED INTO THE LUNG

Nicotine is a tertiary amine derived from tobacco. Of the two stereoisomers, S(-)-nicotine is the more active form. Nicotine binds stereoselectively to acetylcholine receptors in the autonomic ganglia, adrenal medulla, at neuromuscular junctions, and in the brain (2). Nicotine from smoking has an elimination half-life of one to two hours and a volume of distribution of two to three L/kg, which is similar to that from intravenously-administered nicotine. About 80% to 90% of nicotine from smoking is metabolized for elimination, mainly in liver, but also in kidney and lung. A significant fraction of nicotine is metabolized by the lung (3). Major metabolites are cotinine, trans-3'-hydroxycotinine, and nicotine-1'-N-oxide. More than 20 metabolites have been identified, all believed to be less pharmacologically active than nicotine. Importantly, nicotine is a stronger base than its metabolites (4).

Nicotine is readily absorbed from the respiratory tract, buccal mucosa, and skin (5). In habitual smokers, it shows systemic bioavailability of 90% by that route. Nicotine, suspended on minute particles of "tar" in smoking, is quickly absorbed from the lung (almost as efficiently as when given intravenously) (2) and reaches the brain within eight seconds of inhalation.

While destruction of lung tissue by tobacco smoke is irreversible, cessation of smoking slows the rate of decline in pulmonary function so that it begins to resemble that of non-smokers after several years (2). Mortality of inhalers is greater than that of non-inhalers (2).

Nicotine's ability to permeate the oral mucosa has been known since 1932 (6). In addition, nicotine is found to be not only rapidly absorbed across the nasal mucosa from smokeless tobacco snuff placed in the nasal cavity, but also reported to yield the highest plasma nicotine concentration ever reported in man (7,8).

CIRCULATORY DELIVERY OF BIOGENIC AND EXOGENOUS AMINES TO LUNG

Endogenous (biogenic) vasoactive amines (e.g., serotonin, norepinephrine) are taken up from the blood by the lung by a sodium-dependent carrier-mediated transport system operating at the level of the capillary endothelial cell and are then metabolically inactivated (9). The exogenous soluble compounds preferentially localizing in the lung from the blood are basic amines ($pK_a > 8$) having amphiphilic characteristics [i.e., a molecule having a large hydrophobic group with a side chain ionized at physiological pH] (10). Lung uptake of basic amines is saturable, but in contrast to that for endogenous biogenic amines, does not involve a carrier-mediated, energy-requiring transport system.

The lung can efficiently concentrate many exogenous basic amine drugs (e.g, imipramine, methadone, chlorcyclizine, and propranolol) but, in contrast, apparently cannot extensively metabolize them; it merely stores them in a slowly effluxable pool (11). Also in contrast to the biogenic amines, most of the exogenous compounds share a sodium- and energy-independent lung uptake mechanism and persist in the lung at cellular binding sites whose nature and location have not yet been precisely identified (11).

RADIOLABELED EXOGENOUS AMINES

Diamine

One radiolabeled exogenous Diamine, N,N,N'-trimethyl-N'-[2-hydroxy-3-methyl-5-(I-123) iodobenzyl]-1,3-propanediamine (^{123}I-HIPDM), was synthesized years ago by Kung et al. (12,13). It was originally employed clinically for cerebral perfusion imaging. The high lipid solubility of the diamine (partition coefficient in 1-Octanol/pH 7.0 buffer is 40) leads to first pass normal brain extraction of 85% to 95% (14). Iodine-123 retention within the brain is postulated as partly due to (a) a "pH shift," whereby the uncharged molecule at blood pH of ~7.4 ncounters

the intracellular brain pH of ~7.0 which protonates the molecule (i.e., giving it a positive charge), thereby retarding its efflux back through the BBB, and/or (b) specific or non-specific receptor binding within the brain. In the latter part of the postulate, the amines may interact with neuronal or cellular receptors; however, brain uptake and retention of the radiotracer have repeatedly been shown to be independent of carrier dose, refuting a criterion for receptor-specific binding. None of the mechanisms proposed to date fully accounts for the prolonged retention of the radiotracer in brain. A similar situation holds true in the lung, as we shall see below.

Upon intravenous injection in normal human and animals, rapid and diffuse (homogeneous) uptake of ^{123}I-HIPDM in the lungs occurs. The lung images have the appearance of a normal ^{99m}Tc lung perfusion scan. In fact, some of the HIPDM entering the brain comes from the lung pool of drug (14).

Pistolesi and colleagues in Italy have ambitiously looked at many aspects of radioiodine-labeled HIPDM and the lung in human and animals (11,15). For example, lung clearance of ^{123}I-HIPDM in nine normal non-smokers was found to be faster than that in nine asymptomatic smokers of at least 20 cigarettes per day. A bi-exponential curve described lung clearance of radionuclide in both groups. The mean time of the first component(10 $\pm$ 1.4 min.)(mean $\pm$ SEM) in smokers did not differ significantly from that in non-smokers (9.7 $\pm$ 0.9 min). But, mean time of the second component, 12.9 $\pm$ 0.6 hr in the smokers, was almost twice that in non-smokers, 6.7 $\pm$ 0.2 hr. The investigators hypothesized that lung persistence in smokers may reflect either an increased number of cellular binding sites or hindered HIPDM biotransformation (11).

As noted above, lung clearance of ^{123}I-HIPDM in normal man is slow, compatible with relatively stable cellular binding. Normal rabbits receiving ^{125}I-HIPDM intravenously were sacrificed at intervals from two minutes up to five hours post-injection (PI), with lungs excised immediately, weighed, and homogenized. Differential centrifugation of homogenates isolated subcellular fractions (nuclear, mitochondrial, postmitochondrial, and microsomal) and post microsomal supernatant (16). Radioactivity and protein concentration were assessed per isolate. The time-activity clearance curve of ^{125}I in rabbit lung homogenates were comparable to that of ^{123}I-tagged drug measured *in vivo* in humans by external gamma scintigraphy. The ^{125}I HIPDM was recovered only from subcellular fractions of rabbit lung homogenates (nucleus and mitochondria containing the bulk of the compound); the distribution profile mimicked that of arylsulfatase B, a lysosomal marker hydrolase enzyme. Greatest HIPDM specific activity (pmol/mg protein) was in the mitochondrial fraction. HIPDM radioactivity (expressed as percent of total lung activity) in each fraction changed negligibly over the sacrifice-time period evaluated, indicating no redistribution of the diamine among fractions during that period. Overall results suggested that HIPDM in lung is bound to subcellular organelles, with its relative distribution therein indicating that it may be lysosomotropic.

In isolated, perfused rat lungs, ^{125}I-HIPDM uptake by lungs is reduced by concomitant perfusion of either imipramine, propranolol, or chlorpromazine (all lipophilic basic amines), as well as by carrier HIPDM (17). However, addition of ouabain to perfusate or use of a sodium-free perfusate has no effect on lung uptake. ^{125}I-HIPDM does not appear to localize in lung by sodium-dependent active transport. Its uptake appears similar to that of other basic amines (propranolol or imipramine), known to bind by physicochemical interactions to lung endothelial cell membranes and reflect pulmonary vascular surface area.

Using Kung's HIPDM kit with on-site ^{123}I labeling, we (at the VA Medical Center in Lexington, Kentucky) systematically looked at lung uptake of the drug in patients referred to us for routine single photon emission computed tomographic (SPECT) brain imaging. Early-on, we found a case of histologically-confirmed poorly differentiated carcinoma of the lung reflected as a large perfusion defect on the ^{123}I-HIPDM lung image (18,19). The patient was recommended to undergo a course of chemotherapy.

Monoamine

Iofetamine HCl I-123 Injection (SPECTamine, Medi-Physics) was available several years ago for routine (SPECT) cerebral brain perfusion imaging (20,21). This agent is a monoamine, ^{123}I-N-isopropyl-p-iodoamphetamine, known also as ^{123}I-IMP. Again, substantial amounts of intravenously administered drug localized diffusely in normal lungs and liver (22).

RADIOLABELED EXOGENOUS AMIDE

Benzamide Derivatives

A novel group of radioiodinated benzamide derivatives is currently undergoing testing for non-small cell (NSC) lung cancer diagnosis. A prototype designated IPAB ((for ^{123}I-(2-piperidinylaminoethyl)-4-iodobenzamide)) and five related compounds bind specifically to sigma receptors on the cell surface of lung carcinoma cells (23). Normal lung does not express such receptors. SPECT imaging with IPAB of laboratory animals bearing tumors from injected human cancer cells can identify both primary tumors and

metastases. It is also hoped that, eventually, these compounds could possibly treat sigma-receptor containing tumors by delivering anticancer therapies to tumor site(s).

TECHNETIUM-99m CHELATES AND THE LUNG

Diamine Bisoxime

Tc-99m exametazime injection (also known as ^{99m}Tc-d,l-hexamethylpropylene amine oxime, or ^{99m}Tc HMPAO) was introduced several years ago for cerebral perfusion imaging. The ligand and chelate, first described ten years ago by Troutner et al. (24), heralded a new era in clinical brain perfusion imaging. The disadvantages of ^{123}I for SPECT brain imaging could be avoided with this new agent. The HMPAO ligand kit is commercially available under the trade name Ceretec® from Amersham Healthcare.

HMPAO is a diamine bisoxime (i.e., 4 nitrogen atoms available for coordination/molecule) that chelates ^{99m}Tc rapidly into a cyclic structure (after stannous reduction of ^{99m}Tc-pertechnetate). The oxime structure is [(RC(H or R)=NOH)]. The resulting chelate is lipophilic and has a neutral charge (i.e., non-charged); neutrality results from loss of one hydrogen atom from each of the two amine groups and from one of the oxime groups during chelation (25). This so-called "primary lipophilic complex" is present in the injection which has a high pH ranging from 9.0 to 9.8 (26) and can cross the normal BBB. The extraction efficiency across the BBB is estimated at 0.75 (27).

Tc-99m exametazime biodistribution is not restricted to the normal adult or neonate brain in humans (28) upon intravenous administration. The excretory routes and miscellaneous organs are seen on total body scintimages. Focal uptake occurs in a variety of disease states throughout the body. In 1986, two groups (29,30) reported diffuse uptake of radiotracer in the lungs of normal tobacco smokers. Diffuse lung uptake also occurred in a young man with worsening memory loss but unremarkable SPECT brain imaging who had discontinued smoking four days prior to brain (and lung) imaging (28). While the mechanism of such lung uptake (even in the ex-smoker) remains unknown, hypotheses center around several effects on pulmonary vascular endothelium induced by smoking (31).

In a group of 55 patients undergoing SPECT brain imaging for neurologic reasons, it has been reported (32) that the lung/liver uptake ratio of ^{99m}Tc exametazime (calculated by computer on the corresponding lung/liver images) in 30 smokers (0.805 $\pm$ 0.042; mean $\pm$ SEM) was significantly higher than that in the 25 non-smokers (0.408 $\pm$ 0.019)($p < .01$). Liver uptake of tracer is the same for smokers and non-smokers; it was employed for calculating personal ratios.

In habitual marijuana smokers, features of bronchitis are present. In marijuana smokers with or without concurrent tobacco smoking, one finds increased recovery of neutrophils in bronchoalveolar lavage (BAL) fluid, histologic changes comprising squamous metaplasia, goblet cell hyperplasia, and intraepithelial inflammation (33).

A 28-yr-old male polysubstance-abusing marijuana and tobacco smoker had a ^{99m}Tc exametazime lung/liver uptake ratio of 1.325, the highest value we have encountered (Shih W-J, Carmona JJ, Coupal JJ; unpublished observations). The chest radiograph was unremarkable. Delta-9-tetrahydrocannibinol (THC), an isomer of tetrahydrocannibinol, yields most psychological effects from marijuana and is reported to accumulate in the lung (34).

Tc-99m exametazime administered intravenously to 18 patients (youngest of age 38 yr; 14 males) with histologically-confirmed primary lung cancer (35) yielded promising results. Unfortunately, no mention is made of the patients' history of tobacco smoking. In scintigraphic lung images, a region of interest (ROI) was created on computer over the focal lesion with a corresponding ROI created over the same location in the contralateral normal lung. Lung-uptake ratios (lesion/normal lung) of ^{99m}Tc radioactivity indicated significant differences between (a) squamous cell carcinoma (1.2 $\pm$ 0.4; mean $\pm$ SD) and adenocarcinoma (1.6 $\pm$ 0.1) ($p < .05$), (b) large cell carcinoma (0.9 $\pm$ 0.1) and squamous cell carcinoma ($p < .05$), and (c) adenocarcinoma and large cell carcinoma ($p < .01$). Most striking are the relatively homogeneous ratio values (as indicated by low standard deviation values) within the individual histologic types of tumors. Three patterns of tumor uptake of ^{99m}Tc became evident 1) homogeneous (corresponding to tumor), 2) perfusion defect, and 3) ring-like. The latter two patterns often corresponded to necrotic tissue mostly replacing carcinoma cells of tumor. In contrast with ^{67}Ga citrate which accumulated in both malignant cells and necrotic tissue, ^{99m}Tc HMPAO accumulated in only viable carcinoma cells. Perfusion defects corresponding to tumor suggested greater possibility of presence of either squamous cell or large cell carcinoma, rather than of adenocarcinoma. The objective lung uptake ratios (above) tend to support that contention.

Tc-99m exametazime administered to patients with lung tumors (histologic type not specified) yielded high uptake of ^{99m}Tc in all seven of seven tumors (36). In a variety of other primary and secondary tumors (including breast, squamous cell, melanoma, sarcoma, lymphoma), the pattern of perfusion showed a high-activity ring surrounding a low-activity center. In this

brief communication, the authors regard the drug to be useful for detecting tumors in the thorax. In addition, extraction-efficiency of ^{99m}Tc exametazime was greater than that of Rubidium-86 cation (an "ancient," but effective indicator of regional blood flow) in a tumor transplanted in a mouse model. These results indicated greater efficacy of the ^{99m}Tc tracer in showing perfusion to (with likely oxygenation of) malignant tumors. Crucially, this would reveal relative tumor radiosensitivity and consequent options for treatment.

Additional evidence exists for potential use of ^{99m}Tc exametazime as a marker for chemical and external irradiation injury to lungs in man and animals *in vivo*. In a direct dose-dependent manner, oleic acid given intravenously to normal rabbits led to significantly increasing bilateral diffuse lung uptake of subsequently intravenously-injected ^{99m}Tc exametazime (37). While the lowest treatment dose of oleic acid (0.05 mL/kg) led to a significantly increased pulmonary uptake of ^{99m}Tc in all eight rabbits over that in ten control animals (which received no oleic acid), it led to no corresponding reduced pulmonary perfusion sites after intravenous ^{99m}Tc MAA administration. However, in all six rabbits receiving either 0.10 mL/oleic acid/kg or 0.20 mL/kg, ^{99m}Tc perfusion sites in both lungs were reduced or defective after ^{99m}Tc MAA. Electron microscopy of lungs from all oleic acid-treated animals shows morphologic change localized to the microvascular endothelium.

Thirteen patients with lung cancer received a total dose of 16 Gy to 50 Gy (1600 Rad to 5000 Rad) (in 2 Gy increments) during a course of external beam X-ray radiotherapy (37). Only two of the patients (both receiving 50 Gy) showed abnormal opacity on chest X-ray computed tomography (chest CT) due to radiation-related pneumonitis in the irradiated lung; in the remaining 11 patients, there was no corresponding significant opacity in the irradiated lung. All 12 patients receiving more than 30 Gy demonstrated, by SPECT imaging, a higher uptake of subsequently-administered ^{99m}Tc exametazime in the corresponding non-cancerous surrounding irradiated lung than in the contralateral nonirradiated lung. Patients receiving 50 Gy tended to have higher irradiated/nonirradiated lung tracer ratios than did those receiving lower doses. The highest lung activity ratios occurred in the two patients showing an infiltrate on chest CT. Thus, a dose-dependent effect of external-beam radiation therapy to lung was shown by ^{99m}Tc exametazime scintigraphy of lungs; no corresponding sensitivity and specificity were demonstrated by chest CT. An objective quantitative measure of the consequences of irradiation to normal lung tissue by non-invasive scintigraphy suggests its great diagnostic potential in many clinical, sub-clinical, (and perhaps pre-clinical) disease states.

Diamine Dithiol Ligands

A recent development is a group of diamine dithiol (DADT) compounds forming coordinate bonds with ^{99m}Tc (38). The resulting 22 structurally-different chelates are neutral, lipid-soluble, and show varying magnitudes of rapid localization in the lungs of normal mice (up to 31% of the injected dose) at five minutes post intravenous injection.

All are cyclic chelates. The nature and position of various alkyl substituent groups appears to play a role in initial uptake (measured at five minutes) and subsequent kinetic properties (measurements at 15 minutes PI). It appears that partitioning of the respective chelates into the lipid bilayer is not the sole contributing factor to the observed respective percent of injected dose. It is felt that a mechanism of lung uptake sensitive to variations of chelate structure is operating in these living animals.

Lung/liver "selectivity ratios" or ("SRs") comprising [percent injected dose (ID) in excised lungs/gm lungs] divided by [percent ID in excised liver/gm liver], ranged from a high of 15.2 to a low of 0.3 . That particular chelate demonstrating the SR of 15.2 showed only a 13% decline in percent ID from that at five min to that at 15 min; among the other chelates, the average fall was 40% over the period. Relative lipophilicity of the complexes does not appear a major contributing factor to biological half-life of the chelates. The mechanism of binding and pharmaco-kinetics of that unique complex of SR 15.2 may be more involved than that of the others; the authors are evaluating this complex further.

It is felt that evaluation of patients with one of these complexes may prove fruitful in clinical pulmonary diseases such as asthma, emphysema, or lung infection.

Isonitriles

Six isonitrile (-C≡N) ligands chelate a ^{99m}Tc atom forming hexakis-2-methoxy-2-isobutyl isonitrile, known as hexamibi. The chelate bears a single positive charge. It is currently available generically as ^{99m}Tc sestamibi (Cardiolite®, DuPont Pharma). The clinical indication for this agent is myocardial perfusion imaging.

In 11 patients with primary lung cancer, ^{99m}Tc sestamibi has localized in the tumors of ten of the patients as shown by planar imaging (39). Peak concentration of radioactivity in tumor was reached within the first minute of intravenous injection. Tumor/normal lung activity ratios on computer remained constant from five to ten minutes PI to 25 to 30 minutes PI, indicating no washout during that time frame. Using ^{99m}Tc sestamibi SPECT imaging, two other groups of investigators reported sensitivity in detecting primary lung cancer at 91% and 96%,

respectively (40). On a subcellular level, it has been shown that ^{99m}Tc sestamibi binds to a small protein (~10000 daltons) in the cell lysosome.

INDIUM-111 LABELED PEPTIDE

Peptides for scintimaging are prepared from hypervariable regions of antibodies binding to specific cell surface receptor regions (41). Hypervariability indicates that the peptides have antigen specificity similar to that of parent antibody, but reduced affinity for receptor sites, compared with intact antibody (41).

Somatostatin, a neurotransmitter hormone comprising 14 amino acid residues, occurs in human tumors, primarily those displaying amine precursor uptake and decarboxylation (APUD), such as small cell (SC) lung cancers.

[Indium-111-DTPA-D-Phe']-octreotide is a radiolabeled somatostatin analog. It is presently available as ^{111}In-pentetreotide under the trade name OctreoScan® (Mallinckrodt Medical). Its normal tissue localization does not include lung. However, lung uptake may occur after surgery, after external beam radiotherapy to lung, after bleomycin (BLM) treatment, or after upper respiratory tract infections (latter, primarily in pulmonary hilum)(41). In various clinical trials, this radiopharmaceutical has detected SC lung cancer with frequencies ranging from 63% to 100% (41).

NON-MALIGNANT LUNG DISEASE

Respiratory Distress Syndrome

Diffuse alveolar infiltrates are seen on chest X-rays in adult respiratory distress syndrome (ARDS), a clinical disorder of parenchymal inflammation, permeability, pulmonary edema, severe dyspnea, and refractory hypoxemia. The chest X-ray shows progressively increasing lung-tissue density, as accumulation of fluid in the extravascular space replaces gas density with a water-equivalent density. To evaluate lung edema in ARDS best, direct measurement of extravascular lung water is needed (42). However, neither invasive indicator-dilution techniques nor bedside pulmonary angiography or radionuclide perfusion lung imaging is ideal. PET imaging is a more sophisticated method for lung water quantitation (43,44). The chest X-ray is now the only practical means of evaluating pulmonary edema in critically ill patients (42).

Damage to pulmonary endothelium is currently thought to be the first step in evolution of ARDS in patients with sepsis (45). Using noninvasive methods, a 12.8% to 18.8% reduction ($p < .05$) in pulmonary extraction of ^{14}C-5-hydroxytryptamine (5-HT or serotonin) was observed in patients with ARDS compared to that in controls [normal volunteers and patients positive for human immunodeficiency virus (HIV), but without chest symptoms or signs] (45). Notably, subjects "at risk" for ARDS had a 6.2% reduction ($p < .005$) in lung extraction of 5-HT. However, those results had been obtained by invasive techniques. Similarly, first-pass pulmonary extraction of a synthetic amine analog (^{123}I-metaiodobenzylguanidine or MIBG) in sheep receiving endotoxin infusion decreased ($p < .05$) by 27.8% at seven hours and by 42.3% at 24 hours, compared with baseline.

Relevant non-invasive diagnostic techniques, nevertheless, are necessary to ensure widespread clinical acceptance. For example, BLM therapy is known to damage the pulmonary endothelium. Verma et al. (45) sequentially injected intravenously ^{99m}Tc-labeled autologous erythrocytes (as a reference vascular tracer) and ^{123}I-IMP (as an endothelial cell marker) in four patients receiving BLM treatment and in four normal subjects. A mean reduction ($p < .05$) of 28.8% in lung extraction of ^{123}I occurred in the patients, compared with that in the controls. The authors had previously shown that ^{123}I-IMP is extracted from the blood by lung endothelium through a receptor-mediated mechanism. Imaging by gamma camera over lungs and superior vena cava led to a pulmonary-extraction-fraction curve for radiotracer including first pass of tracer bolus and sequentially thereafter. Verma et al. believe that such pilot data on first-pass ^{123}I-IMP pulmonary extraction will lead to similar non-invasive nuclear medicine techniques to evaluate pulmonary endothelial integrity using radiolabeled amine markers for endothelium.

Emphysema

Emphysema is often characterized by disruption of alveolar walls at some site within the acinus, which is the lung division distal to the terminal bronchiole. The acinus includes respiratory bronchioles, alveolar ducts, and terminal alveoli.

Sixteen adult patients of a group of 125 referred for SPECT brain imaging also showed signs of chronic obstructive pulmonary disease (COPD) on their lung images after receiving ^{123}I HIPDM intravenously (46). Decreased radioactivity in the upper one-half or one-third of the lungs indicated so-called mild COPD in ten of the patients, and moderate-to-severe COPD in six. Both anterior and posterior lung images correlated well with changes due to COPD on respective chest radiographs. It is felt that ^{123}I HIPDM lung images may be an ideal diagnostic tool for diffuse pulmonary disease processes.

Current thought on causation of emphysema zeroes

in on the possibility that elastolytic enzymes are released in the lung and, failing to be neutralized, digest the elastic framework (i.e., the protein elastin) of the lung parenchyma (47). Emphysema is almost invariably present in people severely deficient in the globulin known as alpha-1-antitrypsin (alpha-1-proteinase inhibitor, or alpha-1-Pi) which is a potent inhibitor of proteolytic enzymes (such as trypsin and elastase). It is felt that elastase, found in neutrophils and alveolar macrophages, is released therefrom on a more or less continuing basis, to digest the lung parenchyma. When alpha-1-Pi is present, elastase is inactivated in its proteinase activity. Strikingly, the vast majority of patients with emphysema have normal serum levels of alpha-1-Pi. But, the concept of that enzyme-inhibitor balance is still strongly considered to play a role in some cases of emphysema.

Emphysema-like disorders can be induced in animals by intrapulmonary instillation of elastase, papain, or leukocyte homogenates. Intravenous administration of alpha-1-Pi in people naturally deficient in the inhibitor restores the inhibitor-proteinase balance in alveoli. Oxidants(including components of cigarette smoke) can inactivate alpha-1-Pi, rendering it inactive for inhibition of elastase and other proteolytic enzymes.

Shih et al. administered elastase intratracheally in anesthetized normal adult rats (48). Four weeks later, treated and control animals (no elastase) received, sequentially, ^{99m}Tc albumin aggregated (MAA) injection and ^{123}I-HIPDM intravenously 48 hr apart. Elastase-treated animals had a significant decrease in both HIPDM and MAA radioactivity/excised-lung-volume ratios. That suggested a decrease in both functioning pulmonary vascular endothelium and in number of pulmonary capillary vessels caused by enzyme insufflation. The authors suggested a potential for ^{123}I-HIPDM as a diagnostic aid in pulmonary emphysema.

MALIGNANT LUNG DISEASE

Clinically, radiolabeled monoclonal antibodies (MAb) against the oncofetal protein CEA, against human milk fat globulin (HMFG), and against glycoprotein expressed by SC or NSC lung cancers have been evaluated. Around the time that tumor-associated CEA was shown to be expressed in primary lung cancer (49), Goldenberg et al. showed that lung cancer could be imaged by ^{131}I-anti-CEA MAbs (50), the work being done here at the VA Medical Center and the University of Kentucky at Lexington.

Indium In-111 altumomab pentetate (a mouse monoclonal ZCE-025 anti-human antigen CEA antibody (51) has detected 12 of 16 known primary NSC lung carcinomas in 20 patients (52). In that study, six of the patients received 1 mg labeled Mab plus 19 mg unlabeled Mab (total 20 mg), while 14 patients received 1 mg labeled Mab plus 39 mg unlabeled Mab (total 40 mg). That difference was intended to assess if a larger dose of unlabeled Mab would result in higher sensitivity for tumor detection and localization. Clinically, it was learned that there was no difference in tumor detection rate sensitivity between patients receiving either 19 mg or 39 mg unlabeled Mab. Importantly, non-localization of radiotracer in three of four patients with benign conditions suggested its specificity for tumor. Originally described by Haskell et al. in 1983 (53), ZCE-025 is a complete IgG_2 with a molecular weight of 160,000 daltons. It has been evaluated for colorectal cancer imaging as Hybri-CEAker (Hybritech Incorporated); unfortunately, it elicits considerable human anti-mouse antibody (HAMA) production (in > 40% of patients) (54). Levine (55) has succinctly enumerated the negatives of HAMA induction: (a) adverse reactions and possibly death, (b) HAMA interaction with tagged MAb possibly leading to reduced image quality from a HAMA-MAb complex localizing in the liver, thereby also decreasing the amount of desired tagged MAb available for tumor detection, and (c) HAMA interference with some diagnostic tests (e.g., CEA radioimmunoassay).

In a separate study of 66 patients with primary lung cancer, ^{111}In-labeled $F(ab')_2$ fragments of another anti-CEA antibody (F023C5) produced diagnostic images in 57 of 63 patients (90% sensitivity) with histologically-confirmed bronchocarcinoma (56). However, radiotracer localization in non-cancerous lung diseases reduced specificity to 45%. While there were many more lung cancer patients with NSC than with SC studied, lesion scintigraphic detection rates were found to be comparable. A high false-positive rate, coupled with inability to reveal centrally-located lesions smaller than 2 cm (the latter difficulty likely resulting from high background ^{111}In radioactivity) partly led to the limited clinical usefulness of th1s tracer.

Harwood and Abdel-Nabi (57) have recently suggested that smaller MAb fragments tagged with ^{99m}Tc are more likely to yield improved sensitivity and specificity in imaging of lung cancers. NR-LU-10 is a murine antibody of IgG_{2b} subclass that recognizes a glycoprotein expressed on SC lung cancers. In a group of six male patients with pathologically-confirmed SC lung cancer, seven lung lesions were detected (58). Relative success in localizing metastatic disease depended on site (i.e., spread into lymph nodes, bone, and liver was well detected, while that into adrenals and brain was not).

Using the same antibody, Lamki et al. detected 22

of 25 lung lesions (sensitivity 88%) (59). Additionally, two of the patients had pleural effusions, and radiotracer was localized in the fluid. Three occult lesions, later confirmed on follow-up, were also found. In studies conducted by Abdel-Nabi et al. and Lamki et al. (58,59), some of the patients received re-injection of ^{99m}Tc-NR-LU-10 later to assess chemotherapeutic response. In four out of four patients, disappearance of, or a substantial reduction in, lesion radioactivity post treatment reflected favorable clinical and radiographic response to chemotherapy. Thus, ^{99m}Tc-NR-LU-10 appears to not only identify and stage patients newly diagnosed with SC lung cancer, but also effectively monitor response to chemotherapy (57).

A multi-center trial (21 sites) employed ^{99m}Tc-NR-LU-10 to stage SC lung cancer in 96 patients (60). The ^{99m}Tc tracer yielded a positive predictive value of 95 to 100% compared with 96% using the standard battery of tests (e.g., chest X-ray, CT, radionuclide bone scan, bone marrow aspirates, etc.). Fifteen patients initially thought to have disease limited to one-half the chest were upstaged due to detection by radiotracer of previously unsuspected lesions. As a single, non-invasive staging test for SC lung cancer, the ^{99m}Tc MAb fragment had a positive predictive value of 95%, superior to that of any other single test (61).

^{99m}Tc-NR-LU-10 has also shown considerable promise detecting the more-ubiquitous NSC lung cancers. In 44 patients with histological diagnosis of either adenocarcinoma (20 patients), squamous cell carcinoma (13 patients), undifferentiated carcinoma (10 patients), or alveolar cell carcinoma (1 patient) receiving the radiopharmaceutical, images correctly identified 21 of 21 lung lesions, and 10 of 10 mediastinal lesions. Distant metastases were detected with variable efficacy. The radiotracer was found to be more accurate than CT scans in detecting extent of disease, with a positive predictive value of 75% to 100% in patients with metastases in ipsilateral and/or subcoronal lymph nodes and an encouraging negative predictive value of 92% (60). Moreover, as a single agent, ^{99m}Tc-NR-LU-10 is superior to other conventional methods in staging patients with newly diagnosed lung cancer. It also stratifies lung cancer patients well into the appropriate therapeutic regimens which differ qualitatively depending on the histologic diagnosis. As an added benefit, a very low incidence of HAMA formation elicited by NR-LU-10 permits repeated administration of the radiotracer to measure response to therapy. In all, the radiopharmaceutical shows high sensitivity in imaging primary lung lesions and mediastinal involvement.

Accurate imaging of primary lung cancer probably will be achieved by a ^{99m}Tc-labeled MAb fragment rather than by either whole antibody or F(ab')$_2$ fragments tagged with other radionuclides (57). Deletion of the Fc fragment of antibody markedly diminishes induction in the patient of HAMAs and the disadvantages thereof. The prolonged biological half-life of intact MAbs causes delays of two to three days after injection for imaging. Shortened biological half-lives of MAb fragments coupled with the higher photon flux of ^{99m}Tc permit rapid diagnostically-efficient visualization of mediastinal and hilar regions. One-day imaging regimens become possible. Harwood and Abdel-Nabi (57) recently evaluated a ^{99m}Tc-labeled anti-CEA MAb fragment (OncoScint-NSC lung, or Tc-CYT-380 fragment, Cytogen Corporation) in three patients having NSC lung cancers; both primary and mediastinal lesions were detected in all three. Currently in Phase I investigation for NSC lung cancer detection and staging, Tc-CYT-380 fragment is tentatively targeted to receive FDA approval in 1997 (62).

In the long run, radioimmunoscintigraphy with antibody fragments (particularly those tagged with ^{99m}Tc) seems ready to play a dominant role in evaluating people with newly diagnosed lung cancer. Safety, increased sensitivity and specificity, and (probably) cost-effectiveness of such labeled fragments (though nominally expensive to discover and develop) will prove superior to the present grab-bag of tests needed to assess disease extent.

CONCLUSIONS

While ventilatory function and blood vessel patency of lung have been classic nuclear medicine procedures for decades, an exciting array of new radiopharmaceuticals offer potential for our entry into finding and managing lung diseases where nuclear medicine played no effective role in the past.

With a vast surface area that conducts a massive flow of blood, the pulmonary endothelium efficiently metabolizes and/or stores blood solutes in a manner still not well understood. The endothelial cellular and subcellular structures must be examined thoroughly for us to understand their ability to quickly remove radiolabeled amines, amine-oximes, amine-thiols, amides, etc., from blood. Mechanisms of subsequent retention, possible biotransformation, and efflux of the radiotracers remain speculative, while our knowledge of lung ultrastructure is minimal.

The sensitivity of Tc-99m exametazime, for example, to detect subclinical (preclinical?) insult (even long past) to lung in the form of tobacco smoking, chemotherapy, and external beam irradiation offers dramatic diagnostic potential. The possibility of finding and quantitating damage to lung from environmental sources (e.g., radon, "the sick building

syndrome," passive smoking, etc.) holds great promise. With growing acceptance by health physicists of the lung as a radiosensitive organ, our ability to quantify even minimal damage there offers hope.

The radiolabeled peptides, antibodies, and fragments now being evaluated offer greater sensitivity and specificity for receptor binding. Radiolabeling with ^{99m}Tc promotes world-wide acceptance of such products.

We have moved past the concept of the lungs as merely "the plumbing in the chest." We have accepted the fact that the newer radiopharmaceuticals permit us much more scientific and clinical expertise in managing the many structural and/or functional maladies of the human lung which are not now being managed optimally.

References

1. McCuskey RS, Krasovich MA. Anatomy of the Microvascular System. In: Mortillaro NA, Taylor AE, editors. *The Pathophysiology of the Microcirculation.* Boca Raton:CRC Press,1994: 1-18.

2. Chien YW. Recent advances in noninvasive systemic delivery of pharmaceuticals and biopharmaceuticals. *Drug Development & Industrial Pharmacy* 1994;20:417-68.

3. Turner DM, Armitage AK, Briant RH, Dollery CT. Metabolism of nicotine by the isolated perfused dog lung. *Xenobiotica* 1975;5:539-51.

4. Pichini S, Zuccaro P,Pacifici R. Drugs in semen. *Clin Pharmacokinetics* 1994;26:356-73.

5. Benowitz NL. Clinical pharmacology of nicotine. *Ann Rev Med* 1986;37:21-32.

6. Franke FE, Thomas JE. A note on the minimal fatal dose of nicotin for unanesthetized dogs. *Proc Soc Exp Biol Med* 1932;29:1177-9.

7. Temple DJ. The absorption of nicotine from tobacco snuff through the nasal mucosa. *Arch Pharm (Weinheim)* 1976;309:984-7.

8. Russell MAH, Jarvis MJ, DeVitt G, Feyerabend C. Nicotine intake by snuff use. *Brit Med J* 1981;283:814-7.

9. Alabaster VA. Inactivation of endogenous amines in the lungs. In: Bakhle YS, Vane JR, editors. *Metabolic Functions of the Lung*, New York; Marcel Dekker, 1977:3-31.

10. Philpot RM, Anderson MW, Eling TE. Uptake, accumulation, and metabolism of chemicals by the lungs. In: Bakhle YS, Vane JR, editors. *Metabolic Functions of the Lung*. New York; Marcel Dekker; 1977:123-71.

11. Pistolesi M, Miniati M, Petruzzelli S, Carrozzi L, Giani L, Bellina CR, et al. Pulmonary retention of iodobenzyl-propanediamine in humans: effect of cigarette smoking. *Am Rev Resp Dis* 1988;138:1429-33.

12. Kung HF, Tramposch KM, Blau M. A new brain perfusion imaging agent: [I-123]HIPDM:N,N,N'-trimethyl-N'-[2-hydroxy-3-methyl-5-iodobenzyl]-1,3-propanediamine. *J Nucl Med* 1983;24:66-72.

13. Kung HF, Blau M. Regional intracellular pH shift: a proposed new mechanism for radio-pharmaceutical uptake in brain and other tissues. *J Nucl Med* 1980;21:147-52.

14. Kung HF. Iodine labeled brain perfusion imaging agents. In: Nunn AD, editor. *Radiopharmaceuticals-Chemistry and Pharmacology*. New York, Marcel Dekker, 1992:141-65.

15. Miniati M, Cocci F, Paci A, Giani L, Pistolesi M. Evaluation of non-respiratory function of the human lung by HIPDM lung scanning. *Clin Physiol* 1992;12:303-11.

16. Miniati M, Paci A, Ciarimboli F, Cocci, Giani L, Pistolesi M. Lung subcellular distribution of the pneumophilic compound HIPDM [abstract]. *Fed Am Soc Exp Biol J* 1989;3:A1147.

17. Slosman DO, Brill AB, Polla BS, Alderson PO. Evaluation of [Iodine-125]N,N,N'-trimethyl-N'-[2-hydroxy-3-methyl-5-iodobenzyl]-1,3-propanediamine lung uptake using an isolated-perfused lung model. *J Nucl Med* 1987;28:203-8.

18. Coupal JJ, Shih W-J, Brandenburg S. Iodine-123 HIPDM in neoplastic disease of lung: a case report [abstract]. *Abstracts of American Pharmaceutical Association 133rd Annual Meeting*, San Francisco, 1986:92.

19. Shih W-J, Coupal JJ, DeLand FH, Domstad PA, Brandenburg S, Dillon ML, et al. Demonstration of pulmonary mass defect by iodine-123 N,N,N'-trimethyl-N'-[2-hydroxy-3-methyl-5-iodobenzyl]-1,3-propanediamine lung imaging. *Clin Nucl Med* 1986;11:632-3.

20. Hill TC, Holman BL, Lovett R, O'Leary DH, Front D, Magistretti P, et al. Initial experience with SPECT (single-photon computerized tomography) of the brain using N-isopropyl I-123 p-iodoamphetamine:concise communication. *J Nucl Med* 1982;23:191-5.

21. Kuhl DE, Barrio JR, Huang S-C, Selin C, Ackerman RF,Lear JL, et al. Quantifying local cerebral blood flow by N-isopropyl-p-[^{123}I-]iodoamphetamine (IMP) tomography. *J Nucl Med* 1982;23:196-203.

22. Bushnell DL, Eastman G, Barnes WE. Comparison of IMP and HMPAO for SPECT brain imaging. *J Nucl Med Tech* 1991;19:70-4.

23. (Anonymous). Imaging agent for lung cancer and melanoma (RCT Project No. 076B-1646). Research Corporation Technologies, Tucson, AZ, July 1993:1-4.

24. Troutner DE, Volkert WA, Hoffman TJ, Holmes RA. A tetradendate amine oxime complex of Tc-99m [abstract]. *J Nucl Med* 1983;24:P10.

25. Saha GB. *Fundamentals of Nuclear Pharmacy*. 3rd ed. New York: Springer-Verlag, 1992:119-21.

26. Amersham Corporation. Ceretec package insert. Arlington Heights, IL, 1990.

27. Chilton HM, Thrall JH. Radiopharmaceuticals for central nervous system imaging: blood-brain barrier, function, receptor-binding, cerebral spinal fluid kinetics. In: Swanson DP, Chilton HM, Thrall JH, editors. *Pharmaceuticals in Medical Imaging*. New York: Macmillan, 1990:305-42.

28. Shih W-J, Coupal J, Magoun S. The biodistribution of technetium-99m-hexamethylpropylene amine oxime. *Semin Nucl Med* 1994;24:180-3.

29. Sharp PF, Smith FW, Gemell HG. Tc-99m HM-PAO stereoisomers as potential agents for imaging regional blood flow: human volunteer studies. *J Nucl Med* 1986;27:171-7.

30. Costa DC, Ell PJ, Cullum ID, Jarritt PH. The in vivo distribution of ^{99m}Tc-HM-PAO in normal man. *Nuc Med Comm* 1986;7:647-58.

31. Shih W-J, Coupal JJ, Grunwald F, Dillon ML, Biersack HJ. Tc-99m HMPAO lung uptake and cigarette smoking. In: Shih W-J, editor. *Proceedings of the World Chinese Conference of Nuclear Medicine*, Wuxi, China. Chinese American Society of Nuclear Medicine, June 1994:189-94.

32. Shih W-J, Rehm SR, Grunwald F, Coupal JJ, Biersack HJ, Berger R, et al. Lung uptake of Tc-99m HMPAO in cigarette smokers expressed by lung/liver activity ratio. *Clin Nucl Med* 1993;18:227-30.

33. Floreani AA, Buchalter SE, Sisson JH, Thompson AB, Rennard SI. Chronic bronchitis. In: Pennington JE, editor. *Respiratory Infections - Diagnosis and Management*. 3rd ed. New York, Raven Press, 1994:149-92.

34. Hollinger MA. *Respiratory Pharmacology and Toxicology*. Philadelphia, W.B. Saunders, 1985:37-58.

35 Oshima M, Itoh K, Okae S, Tadororo M, Kodama U, Sakuma S. Evaluation of primary lung carcinoma using technetium 99m-hexamethyl propylene amine oxime: preliminary clinical experience. *Eur J Nucl Med* 1990;16:859-64.

36. McReady VR, Tate D, Keeling F, Hammersley PAG, Davidson T, Ott RJ, et al. Technetium-99m HMPAO for the detection of tumours and measurement of blood flow [abstract]. *Brit J Rad* 1988;60:734.

37. Suga K, Uchisako H, Nishigauchi K, Shimizu K, Kume N, Yamada N, et al. Tecnhetium-99m-HMPAO as a marker of chemical and irradiation lung injury: experimental and clinical investigations. *J Nucl Med* 1994;35:1520-7.

38. Lever SZ, Sun S-Y, Scheffel UA, Kaltovich FA, Baidoo KE, Goldfarb H, et al. Pulmonary accumulation of neutral diamine dithiol complexes of Technetium-99m. *J Pharm Sci* 1994;83:802-9.

39. Hassan IM, Sahweil A, Constantinides C, Mahmoud A, Nair M,Omar YT, et al. Uptake and kinetics of Tc-99m hexakis 2-methoxy isobutyl isonitrile in benign and malignant lesions in the lung. *Clin Nucl Med* 1989;14:333-40.

40. Abdel-Dayem HM, Scott AM, Macapinlac HA, El-Gazzar AH, Larson SM. Role of ^{201}Tl chloride and ^{99m}Tc sestamibi in tumor imaging. In: Freeman LM, editor. *Nuclear Medicine Annual 1994*. New York, Raven Press, 1994:181-234.

41. Papathcofanis FJ, Munson L. Peptide radiopharmaceutical imaging. *Appl Radiol* 1994 June;23 (6):11-7.

42. Bombino M, Gattinoni L, Pesenti A, Pistolesi M, Miniati M. The value of portable chest roentgenography in adult respiratory distress syndrome: comparison with computed tomography. *Chest* 1991;100:762-9.

43. Shuster DP, Marklin GF, Mintun MA. Regional changes in extravascular lung water detected by positron emission tomography. *J Appl Physiol* 1986;60:1170-8.

44. Calandrino Jr FS, Anderson DJ, Mintun MA, Shuster DP. Pulmonary vascular permeability during the adult respiratory distress syndrome: a positron emission study. *Am Rev Respir Dis* 1988;138:421-8.

45. Verma RC, Gan M, Bennett L, Lin K, Schiepers C, Basic M, et al. First-pass pulmonary extraction studies in humans [abstract]. *Clin Nucl Med* 1993;18:926.

46. Shih W-J, Lai YL, Coupal JJ, Pulmano C, Wierzbinski B, Dillon M. Detectable chronic obstructive pulmonary (emphysema) disease by I-123 HIPDM lung scintigraphy: animal and human study [abstract]. *J Nucl Med* 1988;29:905.

47. Moser KM, Bordow RA. Chronic obstructive pulmonary disease: definition, epidemiology, and pathology. In: Bordow RA, Moser KM, editors. *Manual of Clinical Problems in Pulmonary Medicine*, 3rd ed., Boston, Little, Brown Co., 1991:219-23.

48. Shih W-J, Lai Y-L, Coupal JJ, Simmons G. [^{123}I]HIPDM pulmonary imaging demonstrates elastase-induced pulmonary emphysema. *Lung* 1993;171:31-41.

49. Said JW, Nash G, Tepper G, Banks-Schlegel S. Keratin proteins and carcinoembryonic antigen in lung carcinoma: an immunoperoxidase study of fifty-four cases, with ultrastructural correlations. *Human Pathology* 1983;14:70-6.

50. Goldenberg DM, Kim EE, DeLand FH, Bennett S, Primus FJ. Radioimmunodetection of cancer with radioactive antibodies to carcinoembryonic antigen. *Cancer Research* 1980;40:2984-92.

51. USAN Council. Monoclonal antibodies - list no. 351. *Clinical Pharmacology & Therapeutics* 1993;54:114-6.

52. Krishnamurthy S, Morris JF, Antonovic R, Ahmed A, Galey WT, Duncan C, et al. Evaluation of primary lung cancer with Indium-111anti-carcinoembryonic antigen (type ZCE-025) monoclonal antibody scintigraphy. *Cancer* 1990;65:458-65.

53. Haskell CM, Buchegger F, Schreyer M, Carrel S, Mach J-P. Monoclonal antibodies to carcino-embryonic antigen: ionic strength is a factor in secretion of antibodies for immunoscintigraphy. *Cancer Research* 1983;43:3857-64.

54. Patt YZ. Radioactive immunodiagnosis (RAID) in patients with colorectal cancer and rising serum CEA. *New Perspectives in Cancer Diagnosis and Management* 1993;1:33-9.

55. Levine G. Investigational radioimmunopharmaceuticals: pharmaceutical care responsibilities and opportunities. *J Pharm Pract* 1994;7:117-23.

56. Biggi A, Bucheri G, Ferrigno D, Viglietti A, Farinelli MC, Comino A, et al. Detection of suspected primary lung cancer by scintigraphy with Indium-111 anti-carcinoembryonic antigen monoclonal antibodies (type F023C5). *J Nucl Med* 1991;32:2064-8.

57. Harwood SJ, Abdel-Nabi H. The use of monoclonal antibodies for radioscintigraphic detection of cancer. *J Pharm Pract* 1994;7:93-116.

58. Abdel-Nabi H, Abrams P, Ackerhalt R, Farrell E, Faubion C, Gona J, et al. Tc-99m-labeled monoclonal antibody imaging of small cell carcinoma of the lung [abstract]. *J Nucl Med* 1989;30:818-9.

59. Lamki LM, Glisson B, Murray JL, Podoloff D, Bhadkamkar V, Salk D, et al. Radioimmuno-scintigraphy of small cell lung carcinoma (SCC) using the Tc-99m labeled monoclonal antibody fragment [abstract]. *J Nucl Med* 1989;30:819.

60. Friedman S, Sullivan K, Salk D. Staging non-small cell carcinoma of the lung using Technetium-99m labeled monoclonal antibodies. *Hematology Oncology Clinics North America* 1990;4:1069-78.

61. Brietz HB, Sullivan K, Nelp WB. Imaging lung cancer with radiolabeled antibodies. *Semin Nucl Med* 1993;23:127-32.

62. Grant KL. Investigational drug tracking: phases I-III and NDA submissions - part II. *Hospital Pharmacy* 1994;29:900-34.

QUESTIONS

1. An element present in many blood-soluble radiopharmaceuticals showing affinity for lung tissue is:

   A. bromine
   B. cadmium
   C. nitrogen
   D. lead

2. A normal never-smoking human would probably show no lung radioactivity on a scintimage of the chest after receiving which one of the following intravenously?

   A. Tc-99m albumin aggregated
   B. Tc-99m exametazime
   C. I-123 iofetamine
   D. I-123 HIPDM

3. An endogenous amine localized in the lungs from blood is:

   A. HIPDM
   B. serotonin
   C. IMP
   D. imipramine

4. In a person with mild COPD receiving I-123 HIPDM intravenously, the lung images would probably show:

   A. intense focal activity at disease site(s)
   B. intense diffuse activity throughout both lungs
   C. a perfusion defect at disease site(s)
   D. no radioactivity present in either lung

5. In normal human cigarette smokers compared with non-smokers, the overall lung clearance rate of the exogenous diamine I-123 HIPDM is:

   A. equal
   B. faster
   C. slower
   D. zero

6. I-123 IPAB binds specifically to which one of the cell surface receptors on NSC lung cancers?

A. epsilon
B. kappa
C. sigma
D. zeta

7. No lung uptake of Tc-99m exametazime would be expected in a:

A. current marijuana and cigarette smoker
B. current cigarette smoker
C. former cigarette smoker
D. never smoker

8. Relative degree of blood perfusion of Tc-99m exametazime to a tumor would likely indicate:

A. relative tumor radiosensitivity
B. relative oxygenation of tumor
C. choice of treatment option(s)
D. all of the above

9. After which one of the following intravenous doses of the liquid oleic acid to normal rabbits were there no reduced or defective areas of lung perfusion following subsequent intravenous injection of Tc-99m MAA?

A. 0.05 mL/kg
B. 0.10 mL/kg
C. 0.20 mL/kg
D. 0.25 mL/kg

10. After which one of the following intravenous doses of the liquid oleic acid to normal rabbits, was there the least lung uptake of subsequent intravenous injection of Tc-99m exametazime?

A. 0 mL/kg
B. 0.05 mL/kg
C. 0.10 mL/kg
D. 0.20 mL/kg

11. HAMA production in patients sometimes occurs after the patient receives:

A. an I-123 labeled basic diamine
B. Tc-99m labeled diamine dithiol (DADT) compound
C. an In-111 labeled antibody
D. an I-123 labeled neutral diamine

12. The site of uptake of radiolabeled basic diamines in the lungs is believed to be in the:

A. muscular layer around each blood vessel
B. blood pool circulating through the lungs
C. the epithelial cells of the arterioles
D. the inner wall of the blood vessel (endothelium)

13. The one study cited investigating subcellular localization of a radioiodinated basic diamine in lungs of normal rabbits demonstrated:

A. considerable redistribution over time of radioactivity from one structure to another
B. greatest diamine specific activity in the mitochondria
C. faster clearance of radiolabel from homogenate fractions *in vitro* than from the different isotopic-labeled compound in lungs of humans *in vivo*
D. no localization of radiotracer in the nucleus

14. Lung extraction from the blood of the radiolabeled endogenous amine serotonin in patients with ARDS is _____ that in patients without:

A. greater than
B. equal to
C. less than
D. virtually undetectable compared with

15. After intravenous injection, I-123 labeled basic amines used as cerebral perfusion (brain) imaging agents tend to localize in normal human lungs:

A. never
B. focally
C. late
D. homogeneously

16. A common quantitative measurement on scintimage of uptake of Tc-99m exametazime in lung tumors may be determined on computer by deriving a "region of interest" activity ratio of tumor-to-:

A. normal brain
B. blood pool (heart)
C. contralateral normal lung
D. thigh

17. The HMPAO molecule contains:

A. 2 sulfur and 2 nitrogen atoms
B. 4 sulfur atoms
C. 4 nitrogen atoms
D. 4 carbon atoms

18. Intratracheal insufflation of the proteolytic enzyme elastase has been used in an animal model *in vivo* for study of:

A. lung cancer
B. respiratory distress syndrome
C. black lung disease
D. emphysema

19. An organ frequently present as the denominator in "activity ratios" or "selectivity ratios" describing lung uptake of blood-soluble radiopharmaceuticals is the:

A. liver
B. kidney
C. spleen
D. heart

20. Therapy with which one of the following drugs described herein has been shown to reduce pulmonary localization of subsequently-injected I-123 IMP?

A. acetylsalicylic acid
B. amoxicillin
C. dipyridamole
D. bleomycin

21. Which of the following statements is true?

A. All lipophilic neutral amine radiopharmaceuticals concentrate in normal and in diseased human lungs.
B. Pulmonary uptake of lipophilic neutral radiopharmaceuticals, when it occurs, is usually rapid.
C. Endogenous (biogenic) amines taken up by the lungs are not metabolized there, but slowly efflux.
D. Exogenous amines are readily metabolized by the lungs with profuse release of metabolites into the blood.

22. Elastase, which may play a role in damaging the structural framework of the lungs, is found in:

A. leukocyte homogenates
B. alveolar macrophages
C. neutrophils
D. all of the above

23. Indium-111 pentetreotide is likely to show greatest diagnostic efficacy for which disease of the lung?

A. emphysema
B. non-small cell cancer
C. ARDS
D. small cell cancer

24. Which one of the following statements is true about Tc-99m NR-LU-10?

A. It has shown promise for detecting both NSC and SC lung cancer.
B. It elicits significant HAMA production in patients receiving it.
C. The Tc-99m label yields poorer quality images than the corresponding I-123 label.
D. As for OncoScint CR/OV, only one injection per patient is recommended.

25. Enhanced uptake of Tc-99m exametazime may be expected in which of the following lung cancer histologies?

A. squamous cell carcinoma
B. adenocarcinoma
C. large cell carcinoma
D. equally among the three above