European Nuclear Medicine Congress 1987 Scientific Highlights

NUCLEAR MEDICINE EXPANDS TO MEET MORE CLINICAL DEMANDS OF PATIENT CARE

"In diagnosing and treating the patient, the physician needs technical skill, scientific knowledge, and human understanding. We should be content with no less. During this congress, we showed how nuclear medicine research contributes more and more to the physician's ability to care for patients and meet various clinical demands."

The European Nuclear Medicine Congress 1987, the fourth and last joint meeting of the two nuclear medicine societies in Europe, was held August 24–28, 1987, in Budapest, Hungary. Dr. med. Dr. rer. nat. Otmar Schober, professor of nuclear medicine, Department of Nuclear Medicine and Biophysics, Medical School of Hannover, Federal Republic of Germany (FRG), summarized the scientific highlights from over 600 abstracts.

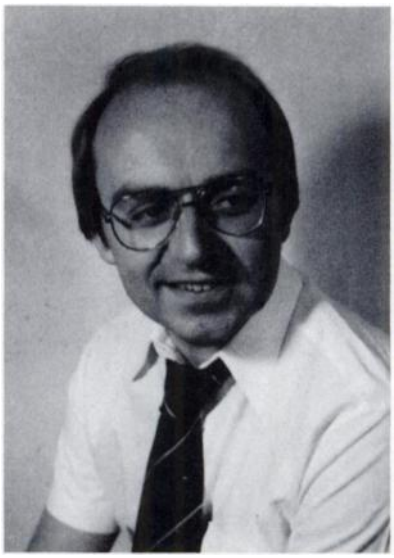
In diagnosing and treating the patient, the physician needs technical skill, scientific knowledge, and human understanding. We should be content with no less. During this congress—with 250 oral presentations, 140 posters with discussion, and 240 posters without discussion—we showed how nuclear medicine research contributes more and more to the physician's ability to care for patients and meet various clinical demands.

Instrumentation

The development of detectors has led us from probes to systems that yield tomographic functional information. Prof. Dr. med. Dipl. ing. Dietrich P. Pretschner, of the Medical School of Hannover, FRG, demonstrated a portable system that performs pathophysiologic studies, such as monitoring renal transplantation (p.143).*

The trend in nuclear medicine, however, is toward tomography. Dr. E. Máté *et al.*, from Prof. László Csernay's group at the University Medical School of Szeged, Hungary, reported on the application of reciprocal matrices in single-photon emission computed tomography (SPECT) (p.46). The inherent scatter and time-consuming reconstruction algorithms, however, remain as obstacles in the steeple-chase to quantify SPECT data.

Filtered back-projection is still not sufficient for good spatial resolution. More accurately iterative algorithms, however, require about one hour of computing time per slice—a problem addressed by Dr. Peter Schmidlin *et al.* of the German Cancer Research Centre in Heidelberg (p.18), and by Dr. H. Luig *et al.* of the University of Göttingen and the Medical University of Lübeck, FRG (p.20).



Prof. Otmar Schober

Grant T. Gullberg, PhD, and colleagues at the University of Utah, the Donner Laboratory of the University of California at Berkeley, and the University of North Carolina, United States (US), modified the time-consuming steps in iterative reconstruction algorithms with respect to parallel processing, which is well suited for hardware implementation (p.21).

Because of the growing importance

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*Abstracts are published (in English) in the August 1987 issue of *Nuklearmedizin*, Journal of the Society of Nuclear Medicine—Europe (*Nucl. -Med* 1987;26:149-190), and are referenced here by page number.

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of a satisfactory dead-time correction for modern block detector positron emission tomography (PET) cameras, Dr. H. Newiger and Dr. Bernd O. Knoop *et al.*, of the Medical School of Hannover, FRG, investigated the influence of the trues-to-single ratio, and gained some basic insights into effects of dead-time in coincident counting (p.85). We need, therefore, iterative algorithms that are suited to those dedicated processors.

A new concept for PET was introduced by a Canadian group. Dr. R. Lecomte *et al.*, of the University of Sherbrooke in Quebec, proposed the use of avalanche photodiodes to replace the cumbersome photomultiplier tubes in the detection system (p.73). We can now expect higher sensitivity, better spatial resolution, and fewer dead-time losses.

I would not encourage the industry to try to improve images by 50% by modifying collimators; I don't think that the future of nuclear medicine lies in a discussion of "step-and-shoot" versus continuous rotation acquisition. The radiopharmaceutical industry has given us tracers that improve the sensitivity of clinical studies more than 10-fold. Nuclear medicine needs ring systems for beta- *and* gamma-emitters because clinical demands show us that one decent functional image is better than 64 poor-quality slices. In addition, time-dependent information is of greater value than a mere 64 frozen or trapped slices.

Dr. Tsanev of the Medical Academy in Sofia, Bulgaria, took one step in this direction with his report on whole-body emission tomography, combining whole-body x-ray computed tomography (CT) with a new type of emission computed tomography performed with a Z-gamma camera (p.18).

The need for rapid "quality control" assessment of camera units has become obvious. Drs. J. Toivanen and A. Rekonen, of the Central Finland Central Hospital in Jyväskylä, presented a study of a quality control system using a personal computer (p.33). This system is portable, permitting measurements in different hospitals.

Extending this idea to SPECT, William J. MacIntyre, PhD, and colleagues at the Cleveland Clinic Foundation in Ohio, US, presented work on computer-controlled SPECT quality assurance (p.34).

Examining the next link in the chain—quality control of the data acquisition system—Dr. J. Vanregemorter *et al.*, of the Experimental Medical Imaging Laboratory at Vrije Universiteit Brussel, Belgium, presented work on a gamma camera simulator (p.34). With this device, microprocessor-controlled tests allow objective evaluation of an acquisition unit that is not connected to a gamma camera. This capability is particularly useful for pinpointing problems in systems built with cameras and computers from different companies, and helps users avoid the situation of one manufacturer blaming the other for the problem.

Quality control of software is a very difficult yet important task, prompting Ellinor Busemann-Sokole *et al.* of the University of Amsterdam, The Netherlands, to quote from the Book of Genesis: "Come let us go down and there confuse their languages that they may not understand one another's speech." This group presented a patient study file, consisting of real or mathematically derived patient data, that can be used as a standardized test on different computer systems to check and compare algorithms (p.35).

Riccardo Guzzardi, of the CNR Clinical Physiology Institute in Pisa, Italy, introduced the European Program on Characterization and Standardization of PET Instrumentation (p.17).

An interesting effort in combining artificial intelligence and image processing was reported by Dr. Z. Szabó and colleagues from the University of Düsseldorf (pp.48,133). These investigations focused on identifying the system transfer function and calculating its parameters. Dr. Szabó showed the vascular transfer function in renal artery stenosis; tubular transit times, for example, were compared with normal values.

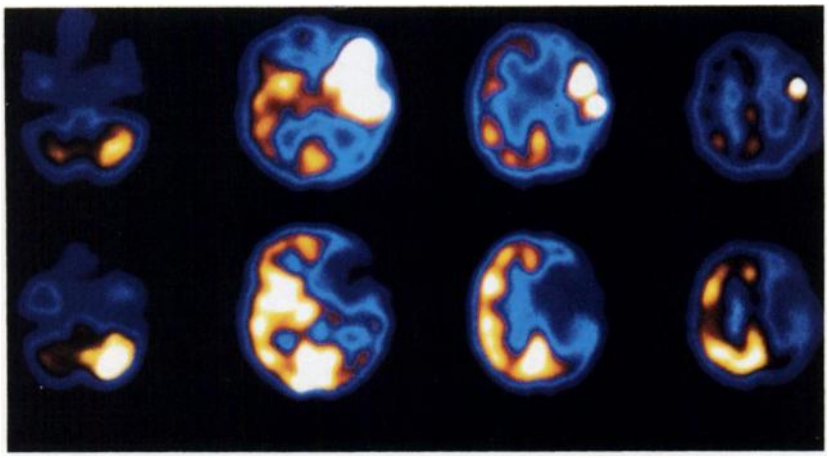

Figure 1. ***These single-photon emission computed tomography (SPECT) studies of regional cerebral blood flow, obtained with technetium-99m hexamethylpropyleneamine oxime (HM-PAO) in a patient with acute stroke, demonstrate luxury perfusion (upper row, day 13) which subsequently resolves into a large area of ischemia and necrosis (lower row, day 40).*** **(Courtesy of Durval C. Costa, MD, and Peter J. Ell, MD: Middlesex Hospital Medical School, London, England)**

Radiopharmaceuticals

There are many exciting advances with technetium-99m hexamethylpropyleneamine oxime (HM-PAO) in neurology, and with technetium-99m-labeled isonitrile compounds in cardiology. During last year's European Nuclear Medicine Congress (held in Goslar, FRG, under the presidency of Prof. Dr. med. Dieter Emrich), many papers dealt with those agents, but most authors presented preliminary results. Now, in some institutions, these agents are used in routine clinical studies.

Durval C. Costa, MD, and Peter J. Ell, MD, *et al.* of the Middlesex Hospital Medical School in London, England, reported that two lipophilic tracers used to measure cerebral blood flow—technetium-99m HM-PAO and thallium-201 diethyldithiocarbamate (DDC)—show different intracellular distributions in the rat brain (p.32). Technetium-99m HM-PAO appeared mainly in the organelles, whereas most of the thallium-201 DDC accumulated in the cytosol.

The trapping mechanism of technetium-99m HM-PAO could be attributed to a rapid *in vivo* breakdown of HM-PAO into secondary hydrophilic, or less lipophilic, components, as suggested by Dr. K. Reichmann and colleagues from the University of Bonn, FRG (p.94).

James L. Lear, PhD, of the University of Colorado Health Sciences Center in Denver, US, compared brain blood flow measurements in rats using technetium-99m HM-PAO, thallium-201 DDC, and a reference tracer, carbon-14 iodoantipyrine (IAP). Autoradiographic studies showed that values with HM-PAO were 60% less than those of the other tracers (p.32). Since the underestimation with HM-PAO is based upon conversion rather than diffusion limitation, both HM-PAO and DDC are suitable for measuring cerebral blood flow in humans with SPECT, according to Dr. Lear.

> "Clinical demands show us that one decent functional image is better than 64 poor-quality slices. In addition, time-dependent information is of greater value than a mere 64 frozen or trapped slices."

A new class of perfusion imaging agents—boronic acid adducts of technetium oxime (BATOs) complexes—was presented by Adrian D. Nunn, PhD, and colleagues from the Squibb Institute for Medical Research, New Brunswick, New Jersey, US (p.43). Three compounds, one for the brain and two for the heart, are now in (or close to) clinical trials. Unlike HM-PAO, washout of the BATOs occurs with a half-life of 90 minutes.

With respect to heart imaging, Dr. med. Klaus P. Kaiser *et al.*, from Prof. Dr. med. Ludwig E. Feinendegen's group at the Nuclear Research Center Jülich, showed that the *ortho* and *para* isomers of iodine-123 phenylpentadecanoic acid (IPPA) behave differently *in vivo* (p.14). *ortho*-IPPA is retained mainly in the cytosolic lipid pool whereas *para*-IPPA is rapidly metabolized through mitochondrial β-oxidation. According to Dr. Kaiser and his colleagues, the difference in mitochondrial acceptance for these isomers might lead to a better understanding of abnormalities in myocardial metabolism, such as cardiomyopathy.

A different approach was pursued by F.F. (Russ) Knapp, Jr., PhD, and associates at the Oak Ridge National Laboratory, Tennessee, US, and the Universities of Bonn and Aachen, FRG (p.14). This group blocked β-oxidation with a β-methyl substitution of *para*-IPPA, and reported that the increased retention would improve SPECT uptake patterns. The slow washout was unexpected, however, and redistribution of the unaltered fatty acid, as well as the washout of unknown metabolites, must be taken into consideration.

Dr. S.-L. Karonen and Kristian B. Liewendahl, MD, *et al.* of the University of Helsinki, Finland, labeled tissue plasminogen activator (tPA) with iodine-131, and administered it to patients with various malignant soft tissue tumors (p.16). Accumulation of iodine-131 tPA was demonstrated in malignant tissues. Since tPA avidly binds to fibrin, a component of the stroma in many malignant tumors, the Helsinki group believes that iodine-131 tPA is taken up by the stroma and not by malignant cells. Carrier-free or inactive tPA should be used; otherwise, the protective cover of the tumor may be destroyed. Radiolabeled tPA could also be of great interest in the follow-up of lysis therapy in coronary artery disease.

Prof. Dr. med. Erich Oberhausen and colleagues at the University Hospital in Homburg/Saar, FRG, presented results of the use of radiolabeled monoclonal antibodies (431/31 and 431/26) in 119 examinations of pa-

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"The emergence of SPECT capabilities for studying dementias and brain tumors points to the growing need for development of a technetium-99m-labeled glucose agent."

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tients with colon cancer (p.51). This group reported the differences in biokinetic behavior among antibodies labeled with iodine-131, indium-111, and technetium-99m.

In light of these results, the biosynthetic labeling of monoclonal antibodies with selenium-75 selenomethionine, presented by Drs. J.-E. Ryser and A. Donath of the Hôpital Cantonal Universitaire in Geneva, Switzerland, is of interest (p.17). These data show that radioiodinated monoclonal antibodies have a shorter half-life and lower recovery of the injected dose compared with the selenium-75-labeled form. There is, however, an unexpected loss of selenium.

Basic Research

The theory and initial results of a method to quantify regional cerebral blood flow with technetium-99m HM-PAO and gold-195m was presented by Dr. O. Nickel and colleagues from the University of Mainz, FRG, (p.93). This group compared the results with values from xenon-133 inhalation, and reported a good correlation.

Dr. S. Mahmoud and Keith E. Britton, MD, *et al.* of St. Bartholomew's Hospital in London, England, used a nondiffusible tracer, technetium-99m human serum albumin (HSA), to calibrate the flow of technetium-99m HM-PAO in the brain (p.93). The group found that the mean measured extraction efficiency of HM-PAO was 49%. Hoping that extraction efficiency is constant for different disease states, the group reported on the clinical benefits of technetium-99m HM-PAO brain blood flow studies in patients with subarachnoidal hemorrhage. Based on serial SPECT studies, surgery was postponed when total cerebral blood flow was below 600 ml/min and regional cerebral blood flow showed defects; surgery was undertaken when total cerebral blood flow improved with time to near normal values.

Results of PET studies with the very optimized fluorine-18 fluroethylspiperone in humans and baboons were presented by Dr. H.H. Coenen and Prof. Dr. rer. nat. Gerhard Stöcklin *et al.* from the Nuclear Research Center Jülich and the Max Planck Institute for Neurological Research, Cologne, FRG (p.102). The tracer is initially distributed in proportion to brain blood flow, but then accumulates in the caudate nucleus, imaging the D_2 dopamine receptors.

In terms of quantity, amino acids are rather unimportant for brain metabolism. The accumulation of amino acids in brain tumors, however, correlates with malignancy. To understand this phenomenon, Dr. Geerd-J. Meyer *et al.* of the Medical School of Hannover, FRG, analyzed amino acid uptake and protein incorporation in rat brain tumors with different isomers of amino acids such as methionine (p.102). These data suggest that transport phenomena govern the uptake process in normal tissue and in tumors, and can be interpreted in close agreement with clinical findings of brain tumors.

Since the health warnings against cigarette smoking are widely known, I was surprised by a paper from Dr. F. Grünwald and colleagues at the University of Bonn that documented the influence of an acute infusion of nicotine on the local cerebral glucose utilization of the awake rat (p.104). Using carbon-14 deoxyglucose and quantitative autoradiography, the group demonstrated distinct increases of glucose uptake in nine of 45 examined brain structures.

There were three times as many presentations on technetium-99m HM-PAO than on iodine-123 iodoamphetamine (IMP). Investigators, however, may have presented more biologic information on the kinetics of iodine-123 IMP. Groups from Vienna, Lille, and Paris compared these blood flow markers.

Dr. N. Vigneron and Jean Luc Moretti, MD, *et al.* of the Hôpital Henri Mondor in Créteil, France, found that the "old-fashioned" iodine-123 IMP offered some advantages in terms of sensitivity for studying cerebrovascular disease (p.117).

Dr. M. Steinling and colleagues from Lille-Cédex, France, reported that the delayed distribution, or "filling-in," of iodine-123 IMP reflects metabolic activity *and* passive diffusion, and cannot, therefore, be used as a cell-viability index (p.150).

Neurology

Neurologists and neurosurgeons require diagnostic information from nuclear medicine procedures, particularly in cerebrovascular disease, the second most frequent cause of morbidity and mortality. They also need

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to detect the occurrence and recurrence of neoplastic diseases. Seizure disorders, as well, can be elucidated with radionuclide techniques. Differential diagnosis of dementia is still a problem; effective methods of early diagnosis and therapeutic follow-up of extrapyramidal syndromes and peripheral neuropathy are still lacking.

During their report on the biodistributions of two brain blood flow agents (p.32), Dr. Costa *et al.* of the Middlesex Hospital Medical School, London, England, presented a demonstration of luxury perfusion in the human brain, evident 13 days after a huge infarction (Fig. 1).

Much more discrete changes were reported by Dr. T. Kuwert *et al.* of the Nuclear Research Center Jülich and the University of Düsseldorf. This group studied cerebral blood flow and metabolism in patients with asymptomatic carotid artery occlusion, which was diagnosed by PET but undetected by transcranial doppler sonography or CT (p.116). Like the symptomatic patients, the asymptomatics compensate for the occlusion with a higher oxygen extraction ratio.

Prof. Dr. med. Udalrich Buell and colleagues, at the Technical University of Aachen, FRG, concluded that blood flow/volume imaging of the cerebrovascular reserve provides more sensitivity than blood flow imaging in cerebrovascular disease (p.93). One problem in expanding this established PET procedure to SPECT, in my opinion, lies not in the pathophysiologic approach but in the inherent limitations of SPECT.

The important task of follow-up to detect recurrent brain tumors was studied by Dr. K.-J. Langen *et al.*, of the Nuclear Research Center Jülich and the University of Düsseldorf, FRG (p.118). Using technetium-99m HM-PAO, this group studied various types of tumors in 40 patients, and found that tracer uptake was variable in malignant gliomas and low for all other tumors. One patient studied during the course of radiotherapy showed a 15% reduction of tumor uptake compared with the cortex.

Technetium-99m HM-PAO also shows potential in differentiating between various types of dementia, and could play a major role in the management of psychiatric patients, according to results from H.G. Gemmell, MD, and associates at the University of Aberdeen in Scotland (p.112). It is possible that SPECT images with this agent will help physicians predict the onset of Huntington's disease in patients genetically at risk, but HM-PAO provides little information in Parkinson's disease.

More optimistic data concerning therapeutic management of patients with Parkinson's disease were presented by Dr. Costa and colleagues at the Middlesex Hospital Medical School (p.111). During L-dopa withdrawal, the caudate nucleus shows a decreased uptake of technetium-99m HM-PAO, whereas the thalamus shows a higher uptake of this agent.

Hallucinating patients also exhibited abnormal brain blood flow patterns with technetium-99m HM-PAO, as reported by E. Suess, MD, and Ivo Podreka, MD, *et al.* from the University Hospital in Vienna, Austria (p.113).

Until recently, studies on neurologic disorders could not be performed without PET. The emergence of SPECT capabilities for studying dementias and brain tumors, however, points to the growing need for development of a technetium-99m-labeled glucose agent.

Endocrinology and Thyroid Diseases

The limitations of thyroglobulin in detecting benign and malignant diseases were pointed out by two groups: Dr. med. Harald Deckart *et al.* of the Klinikum Berlin-Buch, German Democratic Republic (DRG) (p.66); and Andre J. Brendel, MD, *et al.* of the University of Bordeaux, France (p.63).

Dr. P. Peltier and colleagues from Nantes and Gif sur Yvette, France, compared indium-111 antithyroglobulin monoclonal antibodies with the conventional radioiodine scan (p.64). The antibody imaging procedure showed metastases, undetected by iodine-131 studies, in patients with normal thyroglobulin levels.

Dr. L. Manil *et al.* of the Institute Gustave-Roussy in Villejuif-Cédex, France, demonstrated the use of anti-calcitonin monoclonal antibody fragments (labeled with iodine-131, indium-111, and iodine-125) for imaging medullary thyroid carcinomas (p.50).

Cardiology

About 80% of all ischemia, detected by the Holter monitor, is asymptomatic, or "silent." Do these patients need therapy? Nuclear medicine is expected to provide information on flow and metabolism, and to help determine whether there are steal effects in transmural or endocardial diseases.

The ability to measure velocity and flow adds an extra dimension to nuclear magnetic resonance (NMR) imaging. Dr. S.R. Underwood and colleagues at the National Heart and Chest Hospitals in London, England, presented data on the clinical application of NMR velocity mapping (p.58). The field even echo rephasing (FEER) sequence gives a high signal from the blood except where there is turbulance.

Technetium-99m-labeled isonitriles are going to replace the potassium analogue, thallium-201, in heart imaging.

Steven J. Williams, PhD, Shakur A. Mousa, PhD, and their group from Dupont in North Billerica, Massachusetts, US, reported that the

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"Is RP-30 really a blood flow marker, or is it a tracer that reflects oxygen metabolism?"

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specificity for, and the prolonged retention of, the RP-30 compound [technetium-99m hexakis-2-methoxy-2-methylpropyl isonitrile] is caused by a high-affinity association with a cytosolic protein that is sensitive to severe hypoxia (p.55). We know from animal studies that RP-30 is at least as sensitive as thallium-201 for detecting different degrees of coronary artery stenosis (p.56).

Dr. D. Franceschi and colleagues at the Johns Hopkins Medical Institutions, Baltimore, Maryland, pointed out that RP-30 exceeded blood flow in canine studies (p.55). Is RP-30 really a blood flow marker, or is it a tracer that reflects oxygen metabolism?

Because RP-30 does not show significant myocardial clearance, the protocol used for conventional thallium-201 studies must be reversed for RP-30. An injection of a low dose at rest, followed one hour later by a higher dose at stress, is a practical alternative, as reported by Jean Léveillé, MD, Raymond Taillefer, MD, *et al.* of the Hôpital Hôtel-Dieu de Montreal, and the Cardiology Institute of Montreal, Canada (p.56).

Frans J. Wackers, MD, reported results of a collaborative study by investigators at Dupont, Yale University Medical Center, Cedars-Sinai Medical Center, and Massachusetts General Hospital evaluating the biodistribution, kinetics, and dosimetry of RP-30 in 14 normal volunteers (p.56). Several research groups reported comparisons of RP-30 and thallium-201, including: Mary P. Larock, MD, and Pierre Rigo, MD, *et al.*, University of Liege, Belgium (p.57) (Fig. 2); Dr. F. Wackers *et al.* (p.56); Dr. M.N. Maisey, Guy's Hospital, London, England (p.104); and Prof. U. Buell, Technical University of Aachen (p.58).

In his group's study of quantitative stress/rest thallium-201 SPECT, Prof. U. Buell pointed out that parameters such as a regional vitality and a careful redistribution analysis add considerable information in cases of low- and high-grade coronary artery stenosis (p.105).

Using dual-isotope SPECT with rubidium-81 and krypton-81m, Dr. H.P. Stoll and colleagues of the University of Saarlandes, Homburg, FRG, obtained myocardial blood flow measurements in 30 patients (p.118). The group demonstrated that a patient with septal ischemia has a high krypton-81m/rubidium-81m ratio.

The breakdown of the myocardial cell membrane, imaged with a positive contrast scan, is mainly assessed with unspecific markers such as pyrophosphate. Dr. R. Schoening and Prof. Dr. med. Carl Schümichen *et al.* of the Albert-Ludwigs University in Freiburg, FRG, introduced a modified contrast medium, iodine-123 iothalamate (p.71).

Indium-111-labeled antibodies against myosin, however, which accumulate in regions of lowest myocardial blood flow, will eventually replace these unspecific markers. Dr. med. Heinz Sochor *et al.* of the University of Vienna, Austria, reported that a pattern showing low uptakes of both thallium-201 and indium-111 antimyosin after coronary reperfusion suggests salvageable myocardium (p.104). Concordant defect extension demarcates failure of the reperfusion intervention. SPECT studies may provide a tool for better defining infarct zone and salvaged myocardium in patients with reperfusion.

Specificity to myosin, but not specificity in a sense of clinical diagnosis, was demonstrated by Gassett I. Carrió, MD, and colleagues at the Hospital de San Pablo in Barcelona, Spain (p.96). There was no difference in indium-111 antimyosin uptake in active myocarditis compared with graft rejection.

Pulmonary Diseases

The growing incidence of acquired immunodeficiency syndrome (AIDS) has aroused interest in radionuclide procedures developed to detect pulmonary emboli. The simple gallium-67 scan has been rediscovered for initial detection of an opportunistic pneumonia caused by *Pneumocystis carinii*, exemplified by a paper from Dr. K. Tatsch and associates at the University of Munich, FRG (p.107).

To assess lung epithelial permeability with a global test for lung clearance that accounts for mucociliary clearance, Dr. H. Köhn *et al.*, of the Wilhelminenspital in Vienna, Austria, proposed administering technetium-99m diethylenetriaminepentaacetic acid (DTPA) aerosol, and then measuring the excretion of the tracer in the patient's urine (p.97).

The pulmonary surfactant system appears to be a rate-limiting factor for the pulmonary clearance of inhaled technetium-99m DTPA, as reported by Dr. P. Wollmer *et al.* from the University of Lund, Sweden, and Erasmus University in Rotterdam, The Netherlands (p.98).

Gastroenterology

The clinical demands of this specialty encompass the diagnosis of diseases of the small intestine, absorption and bleeding, and regional infiltrative and metabolic liver diseases. The pancreas still presents a diagnostic problem—differentiating

between cancer and pancreatitis in the head of the pancreas. Two breath tests presented at this congress should be mentioned.

For assessing liver function, Drs. H. Faust and P. Krumbiegel *et al.*, of the Central Institute for Isotope and Radiation Research of the Academy of Sciences, Leipzig, GDR, presented a nonradioactive nitrogen-15 methacetin test, replacing the equivalent carbon-14 aminopyrine breath test (p.67).

To detect infection by *Campylobacter pyloridis*, implicated as a causative agent of active chronic gastritis and peptic ulcers, Eric A. van Royen, MD, *et al.*, of the University of Amsterdam, The Netherlands, evaluated a carbon-14 urea breath test, based on a very high urease activity (p.70).

Oncology

The clinical demands from oncology have changed over recent years as scientists and physicians in this field grow more interested in biologic response modifiers. Oncologists are interested in cytokines, and eagerly await tissue- and organ-specific monoclonal antibodies. Oncogenic regulation could be a possibility in the future. Oncologists are more interested in the staging of tumors (with the exception of carcinomas of the colon) than in the detection of recurrence. I am convinced that radiolabeled monoclonal antibodies will provide a way to solve some of the problems that the whole field of oncology faces.

Noting that 50% of patients receiving single injections of murine monoclonal antibody develop human antimurine antibody (HAMA), James C. Reynolds, MD, and colleagues at the National Institutes of Health (NIH) in Bethesda, Maryland, US, reported that antibody imaging or therapy may be effective when HAMA levels are low because most of the injected murine antibody remains uncomplexed (p.21). High HAMA levels may be overcome by using a large quantity of murine antibody.

Comparing the uptake of iodine-125-labeled monoclonal tPA antibody in irradiated and nonirradiated HeLa tumors, Dr. P. Oehr *et al.*, of the University of Bonn, FRG, and SBL in Stockholm, Sweden, reported that immunoscintigraphic images were improved following tumor irradiation, and that a time-dependent increase of activity uptake was observed in the irradiated tumors (p.36).

Before applying this method to routine clinical work, however, we should at least try to obtain a quantitative estimate of antigen concentrations in tumors. Dr. S. Del Vecchio and associates from Steven M. Larson's group at NIH presented a method for determining antigen concentrations in human melanoma by quantitative autoradiography (p.24).

The next step in development should include biokinetics and absorbed doses from antibodies. Prof. Dr. rer. nat. Dr. med. Hans Detlev Roedler *et al.*, of the Institute für Strahlenhygiene des Bundesgesundheitsamtes in Neuherberg and the University of Munich, FRG, stated that immunoscintigraphy with iodine-131 and indium-111 is a procedure with high values of organ dose and effective dose equivalent (p.22). Although the primary concern of oncologic patients pushes concerns about radiation risk to a secondary level, additional improvements in biokinetics—such as furthering the use of technetium-99m—are essential.

A prospective study of the clinical application of iodine-131 F(ab')2 frag-

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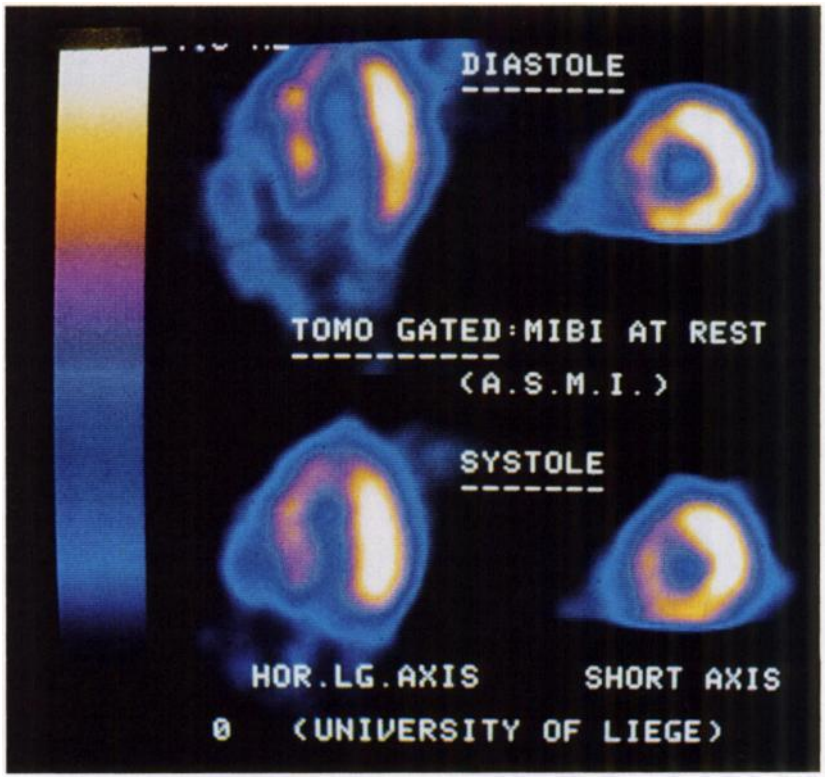

Figure 2. Gated tomography studies obtained with technetium-99m hexakis-2-methoxy-2-methylpropyl isonitrile (RP-30) in a patient with anteroseptal myocardial infarction. The authors observe both a systolic deformation and a lack of thickening of the anteroseptal wall of the left ventricle corresponding to abnormal regional ventricular wall motion.

(Larock MP, Rigo P, Cantineau R: University of Liege, Belgium)

"There is no best diagnostic method for bone/joint diseases. Specific clinical demands require different approaches and, in some cases, complementary imaging procedures provide the best answers."

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ments of anti-carcinoembryonic antigen (CEA) in 70 patients was presented by Dr. med. Richard P. Baum *et al.* from the J.W. Goethe University Hospital in Frankfurt/Main, FRG (p.35). The optimistic results showed that immunoscintigraphy was the only diagnostic method to detect extrahepatic tumor involvement in 20% of these patients.

Using indium-111 anti-CEA in a prospective study of 23 patients with colorectal cancer, Maria Granowska, MD, *et al.*, at St. Mark's Hospital in London, England, observed that normal lymph nodes showed, on average, a five-fold increase in uptake compared with malignantly involved nodes (p.49). With increasing antibody doses, the corresponding higher uptake was seen in both the mucosa and tumor tissue.

SPECT improves the sensitivity and specificity of antibody imaging, observed by Dr. R. Bares and colleagues at the Technical University of Aachen, FRG (p.24). This finding is a bit surprising to me because SPECT requires a lot of photons, but the clinical examples presented by this group were striking.

Dr. G. Leinsinger *et al.*, of the University of Munich, FRG, used SPECT imaging with iodine-131-labeled CA-125 antibody in the follow-up of patients with undifferentiated ovarian cancer to detect recurrences or metastases (p.38).

All of the above-mentioned studies need to be assessed in multicentered clinical trials, such as those described by Jean François Chatal, MD, *et al.* of the Centre René Gauducheau in Nantes Cédex, France (p.38), and by Dr. Gian L. Buraggi *et al.* of the National Cancer Institute of Milan in Italy (p.38).

Many questions still need to be answered about the pathophysiologic parameters affecting antibody uptake, such as blood flow and tumor size. There are also theoretical questions concerning acquisition and statistics. When specificities are significantly less than 100%, how should false positives be handled?

Dr. P-O. Schnell and colleagues at the Karolinska Hospital in Stockholm, Sweden, reported on the contributions of scintigraphy with indium-111 lymphocytes in the staging procedure of Hodgkin's disease (p.51).

Hematology

In hematology, technetium-99m HM-PAO is replacing gallium-67, technetium-99m nanocolloid (in some cases), and indium-111 for detection of infectious diseases because of the availability of the radionuclide, the image quality, and the dosimetry. Four groups have done studies comparing these tracers.

Dr. M. Vorne and associates at the Paijat-Hame Central Hospital in Lahti, Finland, suggested that technetium-99m HM-PAO is superior to technetium-99m nanocolloid and gallium-67 in the detection of inflammatory diseases (p.90).

High-quality images, positive for inflammatory diseases, were presented by: Prof. Schümichen *et al.*, of the

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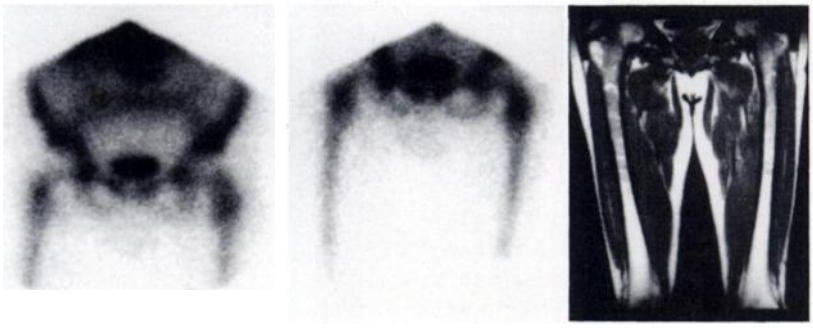

Figure 3. Bone marrow scintigraphy studies (left and center) and nuclear magnetic resonance (NMR) images (right) in a patient with malignant lymphoma. Expansion of the reticuloendothelial system, observed by scintigraphy, and signal decrease, observed by NMR [relaxation time (TR) = 450 ms, echo time (TE) = 30 ms], reveal different information about functional and morphologic abnormalities.

(Widding A, Smolorz J, Franke M, Waters W, Diehl V, Schicha H: University of Cologne, Federal Republic of Germany)

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Dr. D. Lui and colleagues at the Middlesex Hospital Medical School, London, England, confirmed these findings with simultaneous acquisition of white blood cells labeled with both technetium-99m HM-PAO and indium-111 (p.91).

Using SPECT images made with iodine-123 anti-CEA monoclonal antibody, which reacts with a surface glycoprotein of granulocytes, detection of an infected prosthesis was demonstrated by Dr. med. Klaus Seybold *et al.* from the Federal Institute for Reactor Research in Würenlingen, Switzerland (p.25).

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Nephrology

The clinical demands from nephrologists vary from diagnosing patients with chronic impairment in parenchymatous disease to erythropoietin treatment. Despite recent developments, scintigraphy is only occasionally used in hospitals to diagnose suspected renovascular stenosis. There has been a great effort directed toward evaluating Captopril renography in this differential diagnosis. There are side effects, however, after ACE [angiotensin converting enzyme] inhibition, and I am not sure if this test is appropriate for screening.

Dr. A. Meyers and colleagues from the University of Liege, Belgium, presented optimistic data on the use of Captopril renography to evaluate renal artery stenosis and predict the postoperative outcome (p.27). Reporting less optimistic results, Dr. J. Šuštaršič *et al.* of the University Medical Centre Ljubljana, Yugloslavia, concluded that the diagnostic value of these tests is not superior to history data and physical findings, and that the available techniques, particularly renal perfusion scintigraphy, need to be further refined (p.28).

I will be more convinced when evaluations and thresholds are better defined. One step in that direction was demonstrated by Dr. C.C. Nimmon and colleagues at St. Bartholomew's Hospital in London, England. This group compared the frusemide response with parenchymal transit time in the differential diagnosis of obstructive nephropathy, and concluded that quantitative analysis of both parameters improves the evaluation (p.29).

Keith E. Britton, MD, and his group at St. Bartholomew's Hospital, London, presented results of a clinical trial to assess the effectiveness of technetium-99m mercaptoacetyltriglycine (MAG3) for routine renal studies, and concluded that the agent is suitable for this purpose (p.26). Compared with iodine-131 orthoiodohippurate (OIH), technetium-99m MAG3 has a similar biologic half-life, a smaller volume of distribution and, therefore, a slower rate of clearance.

But we must take into account one problem, pointed out by Dr. W. Brandau and colleagues at the University of Heidelberg, FRG (p.29). During normal preparation of technetium-99m MAG3, the impurity level is 7%, and this group believes that only 99% pure MAG3 [purified by high-pressure liquid chromatography (HPLC)] should be regarded as suitable for routine human studies.

Bone/Joint Diseases

Comparing leukocyte scanning with three-phase bone scintigraphy in patients with osteomyelitis and infected hip endoprostheses, Dr. A. Hotze *et al.* at the University of Bonn and the University of Erlangen, FRG, demonstrated that improvements in sensitivity and specificity can be achieved by leukocyte imaging (p.100). Are leukocytes better than the old-fashioned phosphonates?

Dr. K. Streule *et al.* at the Univer-

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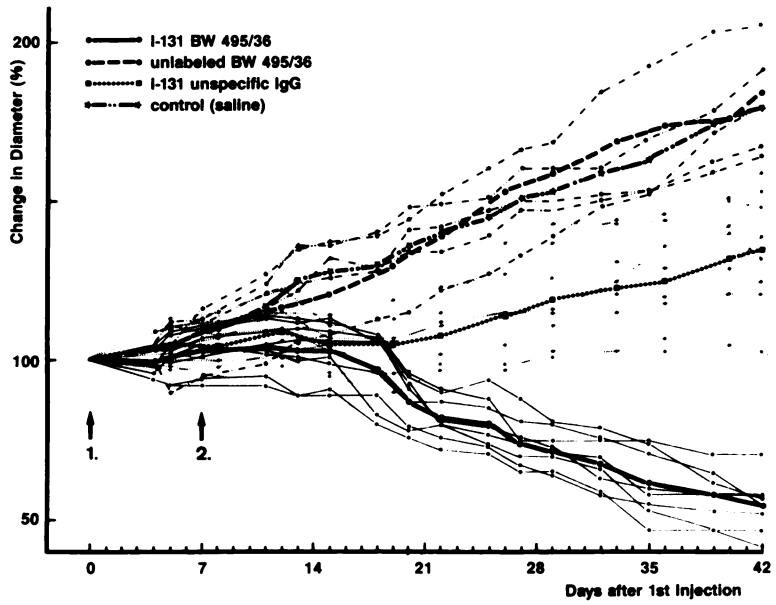

Figure 4. Changes in tumor size of human mammary carcinoma xenografts during the first 42 days after injection of: iodine-131 BW 495/36 monoclonal antibody (MoAb); unlabeled BW 495/36 MoAB; iodine-131 unspecific IgG MoAb; and saline (control). **(Senekowitsch R, Glässner H, Reidel G, Möllenstädt S, Kriegel H, Pabst HW: Technical University of Munich, Federal Republic of Germany)**

COMMENTARY

LINES FROM THE PRESIDENT: RADIODIAGNOSTICS, DRUGS, AND THE FDA

B. Leonard Holman, MD

The date is some time in early October, 1987. Clinical trials of a new iodine-123-labeled brain perfusion agent began in the summer of 1981, more than six years ago. As of today, not one iodine-123- or technetium-99m-labeled tracer has been approved by the United States (US) Food and Drug Administration (FDA) for imaging brain perfusion, metabolism, or receptor function. At this point, the US may be the only nation in the world that does not allow physicians to order state-of-the-art brain scans except as investigational studies.

In 1984, the isonitriles became the first technetium-99m-labeled complex to successfully image the human heart. Since that time, at least three generations of isonitriles have been tested in humans, each with progressively superior biologic characteristics. The isonitrile complex can be altered by an almost limitless number of chemical twists and turns. But each time the chemical form is changed, each time the complex is altered in the slightest, studies of toxicity, dosimetry, biodistribution, and safety—as expensive and exhaustive as for the first isonitrile—must be performed if the new complex is to be tested clinically in the US.

If we are not careful, we may see the end of the commercial development of radiodiagnostics within our professional lifetimes. The expense of bringing these products to market may soon exceed the revenues they generate. Radiodiagnostics are not as profitable as pharmaceuticals since they are used only once or twice in a patient's lifetime. The obvious big winners—technetium-99m-labeled myocardial and brain perfusion agents, tumor agents, and perhaps one or two others—are being developed today. The vast number of radiodiagnostics that are being synthesized and tested throughout the research community—as exciting as these tracers are—have increasingly limited appeal to industry because commercial development costs are too great and large-scale application is too problematic.

The Society of Nuclear Medicine (SNM), along with its sister organizations, has championed increased efficiencies within the FDA and more rapid turn-around times for

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sity Hospital in Basle and Solco Basle Ltd., Switzerland, concluded that bone marrow scintigraphy with technetium-99m nanocolloid is as effective as indium-111 leukocyte imaging for detecting osteomyelitis, and that the bone marrow procedure offers some advantages over the leukocyte scan (p.99). This group calls bone marrow scintigraphy "the poor man's inflammation scan." Is nanocolloid better than leukocytes?

Three groups reported on NMR investigation of the bone marrow system. Drs. H. Stettmeier, R. Bauer, and colleagues at the Technical University of Munich, concluded that NMR can show bone involvement in metastatic cancer sooner than scintigraphic studies of bone or bone marrow, which do not detect small cold lesions (p.62). Is NMR better than bone marrow scintigraphy?

Drs. A. Widding and Prof. Dr. med. Harald Schicha *et al.*, of the University of Cologne, FRG, showed that, in patients with malignant lymphoma or plasmocytoma, NMR signals do not always correspond to tumorous involvement of the bone marrow (Fig. 3); in some cases, these pathologic NMR signals may be caused by compensatory hematopoietic proliferation (p.62).

There is no best diagnostic method for bone/joint diseases. Specific clinical demands require different approaches and, in some cases, complementary imaging procedures provide the best answers.

Therapy

Ethiodol is retained in hepato-cellular carcinoma longer than in normal liver tissue. Dr. Matthew L. Thakur, PhD, and colleagues at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania, US, proposed treating liver tumors with 10–25 mCi (370–930 MBq) of iodine-131 ethiodol, and reported that the tumor receives about an 8,000-rad (80-Gy) dose (p.15). This group demonstrated that the cold spot on a conventional colloid scan is filled in after iodine-131 ethiodol injection; 90

drug approvals. The Inter-Society Commission on Radiopharmaceuticals, under the chairmanship of Alex Gottschalk, MD, has made a great deal of progress toward formulating recommendations to improve the FDA's response to the nuclear medicine community. The FDA has expressed its willingness to implement as many of these recommendations as it can; since our meeting last year with the FDA commissioner, there have been indications of some progress (see *Newsline*, Jan. 1987, pp. 1–11). The SNM and its sister organizations must continue to work with the FDA to insure that technology transfer to clinical practice occurs as rapidly as possible within the limits of FDA regulations and without compromising patient safety.

The fact remains that rapid turn-around of radiodiagnostic new drug applications (NDAs) does little good if no NDAs are being filed—a tragic outcome given the plethora of radiotracers that are being investigated in the field today. The basic problem we face, of course, is that our radiodiagnostics are treated under a set of regulations that have been formulated to test safety in pharmaceuticals with pharmacologic effects and toxicities that may be orders of magnitude greater than our radiotracers. We need less stringent regulations so that we can sift through the vast numbers of radiodiagnostics available to us and narrow our search to the most promising. By narrowing the field and obtaining at least preliminary data on utility, we could far more efficiently determine the radiodiagnostics most suitable for commercialization.

We must streamline the process by simplifying the testing of radiodiagnostics once one compound in a class has undergone the scrutiny of existing FDA regulations. Once one compound in the isonitrile family, for example, has undergone the extensive toxicology, dosimetry, and safety studies required for a Phase I investigational new drug (IND) study, subsequent isonitriles no longer need testing in two animal species and toxicology requirements could be substantially reduced. Furthermore, the supervision of the subsequent studies should be in the hands of the institutional radioactive drug research committees (RDRCs). These hospital-based review committees operate as arms of the FDA, and are fully qualified to evaluate the adequacy of the INDs for subsequent radiodiagnostics after the first compound has passed muster following the traditional pathway. The FDA would be saved reams of paperwork, and researchers in the field could more effectively search out the most promising analogues within a class of radiodiagnostics.

If we are to successfully argue for a streamlined screening procedure for radiodiagnostics, we must be able to carefully document the changes in FDA regulations that would accomplish our goals. These changes must stand the scrutiny of the academic as well as the regulatory community. It seems likely that we will have to press for changes in the regulatory process in the legislative, rather than the regulatory, arena. Ultimately, the US Congress will decide whether the radiodiagnostics and radiotracers that excite all of us at our scientific meetings will ever see the light of day in routine clinical use.

B. Leonard Holman, MD
President, The Society of Nuclear Medicine

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hours later, the agent is cleared from the normal liver but not from the hepatoma.

Prof. Dr. med. Helmuth Rösler and associates at the University of Berne, Switzerland, presented data showing that hyperthyroidism in autonomously functioning thyroid nodules is nonlinearly dependent on size (p.64).

This last paper that I will mention is truly one of the highlights of this congress. The therapeutic effects of an iodine-131 monoclonal antibody, which has a tumor uptake of 50% and a tumor half-life of five days, was evaluated for the treatment of human mammary carcinoma xenografts in nude mice by Dr. Reingard Senekowitsch *et al.* of the Technical University of Munich, FRG (p.52). A 15-MBq (0.4-mCi) dose of this labeled antibody, delivering an estimated 50-Gy (5,000-rad) dose to the tumor, resulted in a "dramatic" reduction in tumor size; mice treated with the same amount of unlabeled antibody, with the same amount of radioactivity from an iodine-131-labeled unspecific antibody, and with saline did not show a comparable reduction in tumor size (Fig. 4).

In histologic sections of tumor tissue obtained seven to 42 days after treatment, marked areas of necrosis were seen; by day 42, most of the tissue was identified as mouse connective tissue. No signs of damage to the bone marrow were observed. These exciting results indicate the possibility that therapy with a specific iodine-131-labeled monoclonal antibody could destroy human tumors without any side effects.

Otmar Schober

More Next Month

The January 1988 issue of *Newsline* will include more information on the European Nuclear Medicine Congress 1987, held August 24–28 in Budapest, Hungary, and an updated report on the new European Association of Nuclear Medicine.