was associated with the cholesterol ester fraction. Subsequently, it was found that these radioiodinated cholesteryl esters were very poor substrates for adrenal cholesteryl ester hydrolase. Thus, in the rat 19-radioiodinated cholesterol was mimicking natural cholesterol by becoming esterified, but its retention in the adrenal was largely due to the inability of these esters to be hydrolyzed back to free radioiodinated cholesterol for subsequent metabolism. This pathway into the storage ester form was further augmented by the inability of radioiodinated cholesterol itself to undergo cholesterol side-chain cleavage, the rate-limiting step in the conversion of cholesterol to the corticosteroid hormones. In man, this overall process of selective retention of radioiodinated cholesterol in the adrenals usually requires 3–5 days before it is possible to obtain high quality images. In order to overcome this time lag, more recent efforts in our laboratory have been aimed at achieving a more rapid localization of radioactivity in the adrenal to permit the use of iodine-123 and single photon computed tomography (SPECT). These studies have taken two directions: the first has involved an analysis of the involvement of plasma lipoproteins as carriers for radioiodinated steroids, and the second has centered on the synthesis of new agents that would be expected to be better participants in a lipoprotein receptor-mediated uptake by the adrenal and associated tumors. The biodistribution properties of several of these newer agents will be discussed.

《招待講演 (3)》

Current Status and Future Developments of Radiopharmaceuticals

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ECT imaging is now proving to be a valuable imaging method, and further improvements in this technique will increase the demand for new agents labeled with short and intermediate half-life radionuclides such as Tc-99m, I-123, In-111, Ga-67, Ru-97 and Pb-203. For "first transit" imaging of the heart, great vessels or other organs, generator systems for ultra-short lived gamma emitters (e.g. 30 second Au-195m from the 40 hour parent Hg-195m) hopefully can be improved. The new Tc-99m agents which localize in the normal myocardium such as methoxy isobutyl isonitrile (MIBI) appear promising as a substitute for Tl-201, and should make it possible to perform ECT imaging of the heart with EKG gating.

In the past, many radiolabeled agents have been evaluated for imaging thrombi and emboli with mixed success. A recent one, promising experimentally, is fibrin fragment E_1 labeled with I-123. Platelets labeled with In-111 oxine or tropolone have successfully demonstrated fresh thrombi up to 24 hours old but their accumulation diminishes rapidly thereafter. In-111 anti-platelet monoclonal antibodies such as P-256 label platelets in vivo after direct intravenous injection and localize well at least in recent thrombi. Other monoclonal antibodies have been developed with which are specific for human fibrin which do not bind fibrinogen. These monoclonals labeled with In-111 demonstrate both fresh and older thrombi on camera images experimentally. Anti-fibrin monoclonal 59D8 Fab fragment and monoclonal T2G1S $F(ab')_2$ fragment labeled with In-111 are now undergoing human trials for thrombus detection.

Lipophilic gamma-emitting agents have been developed which diffuse readily into the brain after intravenous injection for ECT imaging. N-iso propyl-paraiodoamphetamine—I-123 initially reflects regional cerebral blood flow but redistributes over several hours, probably reflecting amine

metabolism. Several Tc-99m lipophilic complexes also have been synthesized for this purpose. One of these, hexamethyl propyleneamine oxime (HM-PAO) remains fixed in the brain and reflects regional differences in cerebral blood flow. Another agent of this type, ethyl cysteinate dimer (ECD) may be a better agent, because of its greater chemical stability.

In nephro-urology, a new agent, Tc-99m mercaptoacetyl triglycine (MAG_3) has been developed as a substitute for I-123 or I-131 hippuran. Its renal clearance is greater than that of Tc-99m DTPA but only about 70% of hippuran clearance. Nonetheless, it produces superior images of kidneys. Metaiodobenzylguanidine labeled with I-131 or I-123, developed at the University of Michigan as an analogue of norepinephrine, has proven effective for imaging adrenal and extra-adrenal pheochromocytomas and certain neuroblastomas and in some instances of other apudomas.

A device was invented in Australia for rapidly incorporating Tc-99m into carbon vapor particles with a uniform size of 50 angstroms. When about 50 μg quantities of these particles are inhaled in one or two breaths, images of the lungs are obtained in multiple projections which reflect ventilatory abnormalities at the alveolar level without normal deposition in the tracheobronchial tree. This agent is superior to Xe-133 or Tc-99m aerosols for detecting ventilatory abnormalities. It has been useful particularly in severely ill patients with suspected acute pulmonary embolism.

The lipophilic chelates In-111 oxine or toropolone are now used widely for irreversibly labeling blood cellular components, particularly autologous neutrophils for detecting and localizing abscesses and other focal inflammatory lesions by camera imaging. These agents have been used also for studying the migration of labeled lymphocytes, cultured mononuclears such as lymphokine activated killer cells and natural killer cells in experimental cellular immunology. The most successful Tc-99m agent for labeling leukocytes thus far has been HM-PAO, now widely used in Europe. A few monoclonal antibodies, such as I-131 or I-123 anti-CEA MAb-47 label neutrophils in vivo after direct intravenous injection and successfully image inflammatory lesions.

Progress in the development of radiolabeled monoclonal antibodies for tumor detection has been surprisingly slow, and the clinical results with many have been disappointing. The most successful clinical trials for imaging to date include anti-CEA and 19.9 monoclonals for colorectal carcinomas, B72.3 for ovarian, colorectal and breast carcinomas, OC-125 for ovarian cancer, antibody against the high molecular weight antigen of malignant melanoma, 3F8 for neuroblastoma and T-101 for cutaneous T-cell lymphoma. A few others have successfully imaged non-neoplastic lesions, such as anti-cardiac myosin for myocardial infarcts, myocarditis and cardiac transplant rejection. Many problems remain to be solved, most notably the formation of human anti-mouse immunoglobulins in the host. This immunogenicity may be less with antibody fragments $F(ab')_2$, Fab or Fv. Determining the optimum amount of antibody or fragment to administer has been difficult and has varied with different antibodies. In-111 immunoglobulins usually concentrate in the liver and labeled fragments in the kidneys. Nonetheless, considerable research effort is being expended to overcome these difficulties.

Today, agents containing short-lived gamma-emitting radionuclides are available for outlining the morphology of most of the major organs by gamma camera imaging. The future calls for agents with higher cellular and tissue specificity including receptor-binding agents such as steroids for membrane proteins of specific cell types, radiolabeled antagonists for specific receptors and agents which follow specific metabolic pathways.