I
IMAGING NEURORECEPTORS IN THE HUMAN BRAIN IN NEUROPSYCHIATRIC DISORDERS.

Ninety years after the first measurement of thyroidal uptake of radioiodine to demonstrate decreased or increased function of the gland, it has become possible to assess the activity of neurotransmitters in the living human brain. Two important neurotransmitters in the brain are dopamine and serotonin. After considerable chemical research, the compound found to have the highest affinity for dopamine receptors is carbon-11-N-methyl spiradone. A related drug, spiradone, is used to treat schizophrenic patients in Japan. A similar drug, haloperidol, is used for that purpose in the United States. On May 25, 1983 we were able to carry out the first imaging of a neurotransmitter in a living human being, despite the fact that the dopamine receptor is present in only picomolar quantities within the caudate, nucleus and putamen. The tracer permits assessment of women that in men. We are investigating whether these findings are perhaps related to hormonal factors.

Other research in our laboratory is directed toward the questions of whether there are neuroreceptor abnormalities in patients with Alzheimer's, Parkinson's and Huntington's diseases, schizophrenia, tardive dyskinesia, Tourette's syndrome and depression. We are also planning to study patients with acute and chronic pain states with the new tracer, carbon-11 carfentanil, which has a high affinity for opiate receptors. Animal studies have been completed and we are only awaiting approval of the Food and Drug Administration to carry out the first human studies.

II
RECENT ADVANCES AND CONCEPTS IN NUCLEAR HEMATOLOGY.
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The use of 32P by Lawrence for the treatment of polycythemia vera and leukemia and the use of 59Fe by Hevesy for the study of anemia were the beginnings almost fifty years ago of both Nuclear Hematology and modern Nuclear Medicine using man-made radionuclides. In the forties red cell volume was determined with 32P, plasma volume with 131I, to be replaced in the fifties and sixties by 51Cr and 125I, respectively. At that time 51Cr was also used to measure red cell and platelet survival and sequestration. 59Fe was used as a cohort label to quantity and localize red cell production and destruction and used to investigate iron absorption and metabolism. The use of DF-32P for the measurement of leukocyte and platelet kinetics as well as red cell survival was also introduced in the fifties. The use of 51Cr for measurement of platelet survival and splenic sequestration was superceded in the seventies by imageable 111In, which was also used to label white blood cells. Currently, in the eighties, new advances in nuclear hematology are unfolding through the use of 99mTc and the development of new coupling reagents, receptor-mediated labeling, and labeled monoclonal antibodies.

The use of 99mTc labeled prethinned red cells for blood pool imaging is superior to 99mTc-HSA. In addition to widespread use for imaging cardiac chambers, 99mTc-RBC is also used for the sensitive and specific localization of gastrointestinal bleeding. The 99mTc label is sufficiently stable in vivo for the accurate determination of red cell volume and the in vivo crossmatching of bank blood with possible simultaneous use of 111In-RBC or 51Cr-RBC. Heat treated 99mTc-RBC provides excellent selective imaging of the spleen. While 51Cr-RBC are still used to assess the extent of splenic sequestration in hemolytic anemias, in vivo 59Fe cohort labeling of RBC is superior, providing more rapid and accurate measurement of possible splenic extramedullary erythropoiesis as well as red cell sequestration and destruction. Imaging of erythropoietic sites is most conveniently performed with 111In, even though reticuloendothelial cell as well as immature red cells are labeled. The use of radioiron for selective labeling of erythrocyte precursors is preferable; however, either a specialized high energy scanner for 59Fe or a positron camera for 59Fe or positron camera for 52Fe is required. Noninvasive quantitation of total body mobilizable iron is best performed by measurement of a 6 hour urine collection after intravenous injection of 59Fe-DTPA.

The use of 111In for labeling platelets permits both measurement of survival and imaging of aggregation sites. While oxine (18-hydroxyquinolone) is the most commonly used lipophilic 111In ligand used for both platelet and leukocyte labeling, other chelates, particularly tropolone, may provide some advantages. 111In-platelets are useful in determining platelet kinetics and survival, imaging sites of sequestration-

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particularly evaluation for splenectomy, and imaging thrombi. Monoclonal antiplatelet antibodies labeled with 111In or 123I show promise for imaging thrombi and vascular lesions. 111In-leukocytes are now widely used in a sensitive and specific procedure for acute abscess localization. Oxine is the most popular lipophilic chelating agent for labeling mixed leukocytes for scintillation camera imaging of focal inflammation. Recent experience with tropolone, another indiscriminate lipophilic cell labeling agent, demonstrates its superiority because of its ability to label cells in small volumes of plasma. Procedure time is reduced, injury from washout is eliminated, and subsequent in vivo lung sequestration is avoided, thereby permitting more rapid localization and imaging of granulocytes. A number of continuing efforts to develop a 99mTc cell-labeling agent comparable to the 111In lipophilic chelates have yet to succeed. Significant recent advances include isolation and labeling of specific leukocyte cell types such as granulocytes, lymphocytes, and their specific subsets, in order to study their migration and kinetics in vivo. New techniques of cell harvesting are utilized and more selective ligands for specific cell surface receptors are being developed so as to avoid laborious separation techniques and decrease radiation injury. Current labeling of lymphocytes with lipophilic chelating agents internalizes the radionuclide so that radiation injury of the sensitive lymphocyte is a major problem in the study of its migration. Use of a gamma-emitting agent which binds irreversibly to the cell membrane would reduce radiation of the nucleus. Selective labeling of lymphocyte subsets is required to discover differences in their migration and function in health and disease. Radiolabeled monoclonal antibodies against cell-surface antigens appear particularly promising for selective leukocyte labeling.

The past fifty years in nuclear hematology have encompassed remarkable advances in radionuclide production, instrumentation, radiochemistry, molecular biology, cell receptor, and immunologic techniques. During this entire period, the central guiding and productive motivation of the development of nuclear hematology has been and continues to be the demonstration of human function in health and disease. These demonstrations are permanent advances.

III

DIAGNOSIS AND THERAPY FOR SOLID TUMORS WITH RADIOLABELLED ANTIBODIES AND IMMUNE FRAGMENTS

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Antibodies which are directed against human tumor associated antigens can potentially be used as carriers of radioactivity for in vivo diagnosis (radioimmunodetection) or treatment (radioimmunotherapy) of tumors, including colon, hepatome, cholangiocarcinoma and melanoma. Murine monoclonal antibodies (MOAB), produced by the hybridoma technique of Kohler and Milstein, are replacing conventional heterosera as sources of antibodies because MOAB can be produced in large quantities as reproducible regents with homogeneous binding properties. We have studied human melanoma using MOAB IgG and Fab fragments that recognize the human melanoma associated antigens p97 and high-molecular-weight antigen. Both antigens are found in the membrane of melanomas as much larger concentrations than in normal adult tissues. We have performed radioimmunodetection studies with whole immunoglobulin and have detected 88 of lesions 1.5cm.

We have used Fab fragments for radioimmunotherapy and have found that large doses of radiolabeled antibodies (up to 342 mCi) can be repetitively given to patients without excessive end-organ toxicity. Two of three patients treated with high-dose radiolabeled antimelanoma Fab showed an effect from the treatment. Although both technical and biologic problem remain. The use of promise as a new therapeutic approach to solid tumors that are resistant to conventional therapy (Cancer Treat. Rep., 68: 317-328, 1984).

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