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SUMMARY

In this report, we describe the synthesis of the cis- and trans-iodovinyl isomers of the new ORNL cholinergic-muscarinic receptor ligand, 1-azabicyclo[2.2.2]oct-3-yl α -hydroxy- α -(1-iodo-1-propen-3-yl)- α -phenylacetate ("IQNP"). This agent is prepared in high radiochemical yield, and the racemic mixture shows high specificity and selectivity for the cerebral and myocardial receptors. Since two chiral centers are present in this molecule, it is important to evaluate the importance of the absolute configuration of the two centers on receptor specificity. The tributyltin substrates were carefully separated by column chromatography, converted to the iodine-125 analogues by iododestannylation, and evaluated in rats in vivo. While the "E" (trans) isomer cleared rapidly from the receptor-rich areas of rat brain, the "Z" (cis) isomer showed high uptake in these areas but also high concentration in the cerebellum. In contrast, the E,Z-isomeric mixture showed good uptake and retention in the receptor rich areas. Studies are now in progress to determine the absolute configuration of the chiral centers in these olefinic isomers.

Also described in this report is a description of neutron flux measurements in the hydraulic tube position at the ORNL High Flux Isotope Reactor (HFIR). Also during this period, samples of [I-125]- and [I-131]-labeled racemic "IQNP" were supplied through a collaborative program with the Brookhaven National Laboratory for high resolution autoradiographic studies in rat tissues. In addition, a tungsten-188/rhenium-188 generator was provided for collaborative studies for dimercaptosuccinic acid (DMSA) radiolabeling at the University of Kent and Canterbury Hospital in England.

SYNTHESIS AND EVALUATION OF THE TRANS (E) AND CIS (Z) ISOMERS OF "IQNP"

It has been reported that the cerebellum and heart contain a high population of the M_2 receptor subtype as compared to M_1 receptor subtype. We reported earlier the development of a new high affinity muscarinic antagonist, 1-azabicyclo[2.2.2]oct-3-yl α -hydroxy- α -(1-iodo-1-propen-3-yl)- α -phenylacetate(IQNP,1)(ORNL/TM-12110,-11881 and-11992). This agent is radiolabeled in high yield with high specific activity and demonstrates high specificity and selectivity for cardiac and cerebral muscarinic acetylcholine receptors (m-AChR). IQNP (1) contains 2 chiral centers; the 2 position on the acetate moiety and the 3 position on the quinuclidinyl moiety, in addition to the orientation of the iodine on the double bond (Figure 1) and therefore contains eight potential isomers.

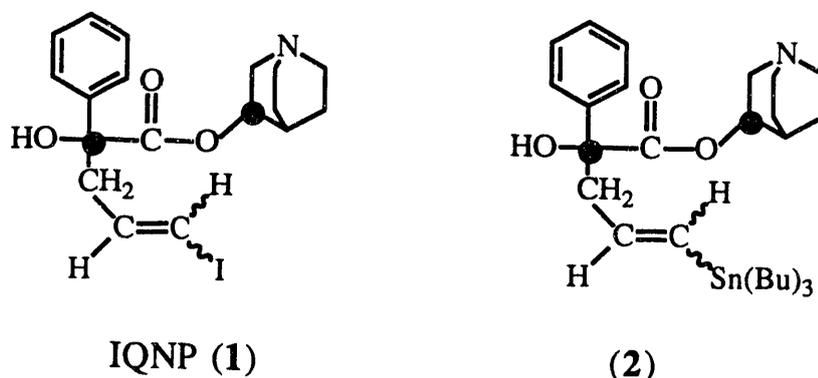


Figure 1. Structures of IQNP(1) and the tributyltin substrate (2)

We have initiated separation of these isomers to determine the best isomer for future kinetic, metabolic and imaging studies. The synthesis of the IQNP involves the preparation of the tributylstannyl intermediate (2) and TLC analysis of 2 indicated two components of similar R_f . NMR analysis of 2 indicated that this was a mixture of the E and Z isomers. Iodination of 2 resulted in 1, which chromatographed as a single component by TLC, but NMR analysis indicated this consisted of the E and Z isomers. HPLC analysis of 1 indicated that the product contained 2 components of equal amounts. After repeated flash column chromatographic purification of 2, three different compounds were isolated. NMR analysis indicated that the first isolated component was the "E-2" ($R_f=0.31$), the second compound was observed to have mainly the E configuration with a slight amount of Z isomer present ($R_f=0.27$), and the third contained Z-2. These isomers were then iodinated and the products analyzed by TLC, NMR, and HPLC. In all

cases the NMR analysis of each compound was identical to the racemic mixture except in the vinyl region where the difference in isomers could be detected. The first compound, "E-1", was isolated as a white solid, mp, 118-119°C, $R_f=0.35$. NMR analysis of the vinyl regions shows a multiplet at 6.50 ($J = 6.35$ Hz) and a doublet at 6.20 ($J = 14.57$ Hz). The second compound, "E,Z-1", was isolated as a white solid, mp, 150°C, $R_f=0.34$. NMR analysis of the vinyl regions shows a multiplet at 6.50 ($J = 6.35$ Hz) and a doublet at 6.20 ($J = 14.57$ Hz) in addition to a multiplet at 6.30 corresponding to a "Z" configuration. The third compound, "Z-1", was isolated as a pale oil, $R_f=0.32$. NMR analysis of the vinyl regions shows a multiplet at 6.37-6.22. HPLC analysis of these isomers indicated that these were three distinct compounds with "E-1" eluting first, "E-Z-1" eluting next and "Z-1" eluting last.

These isomers were then radiolabeled with iodine-125 and their uptake in selected tissues was evaluated in female rats. The results of these studies are shown in Figures 2-4. Initial uptake of "E-1" was high, but cleared rapidly from the areas of interest (Figure 2). "E,Z-1", however, demonstrated substantial uptake in the cortex, striatum, and hippocampus, which are rich in muscarinic receptors (Figure 3). In addition, uptake of activity in the cerebellum (receptor poor) was low after 6 hours, with a cortex to

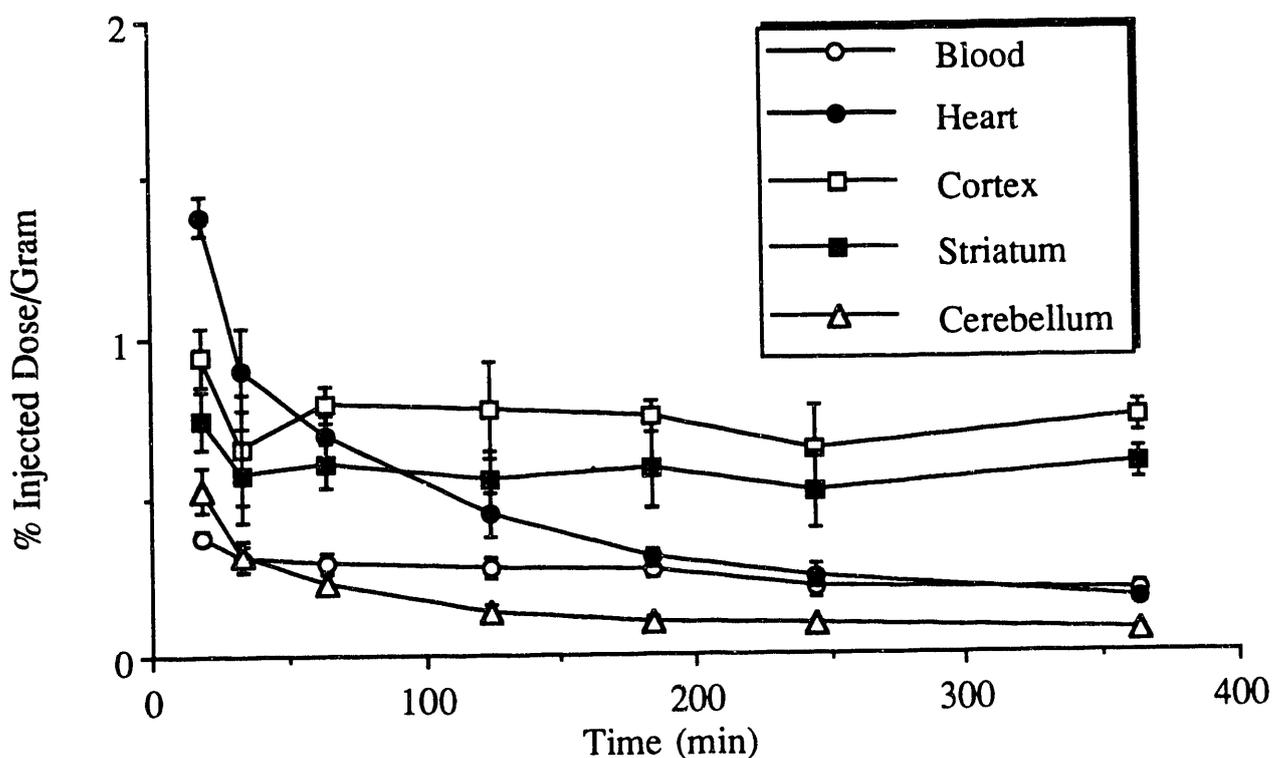


Figure 2. Biodistribution of "E-1" in female rats.

cerebellum ratio of $\sim 20:1$. The uptake of activity in the heart rapidly cleared during the time course of the experiment. "Z-1" demonstrated similar uptake in the cortex, striatum, and hippocampus as was observed for "E,Z-1", however, it also demonstrated higher uptake in the cerebellum (Figure 4). It was also observed that the cardiac uptake of this isomer was higher than that observed for the "E,Z-1" isomer with a heart to blood ratio of $\sim 3:1$ after 6 hours.

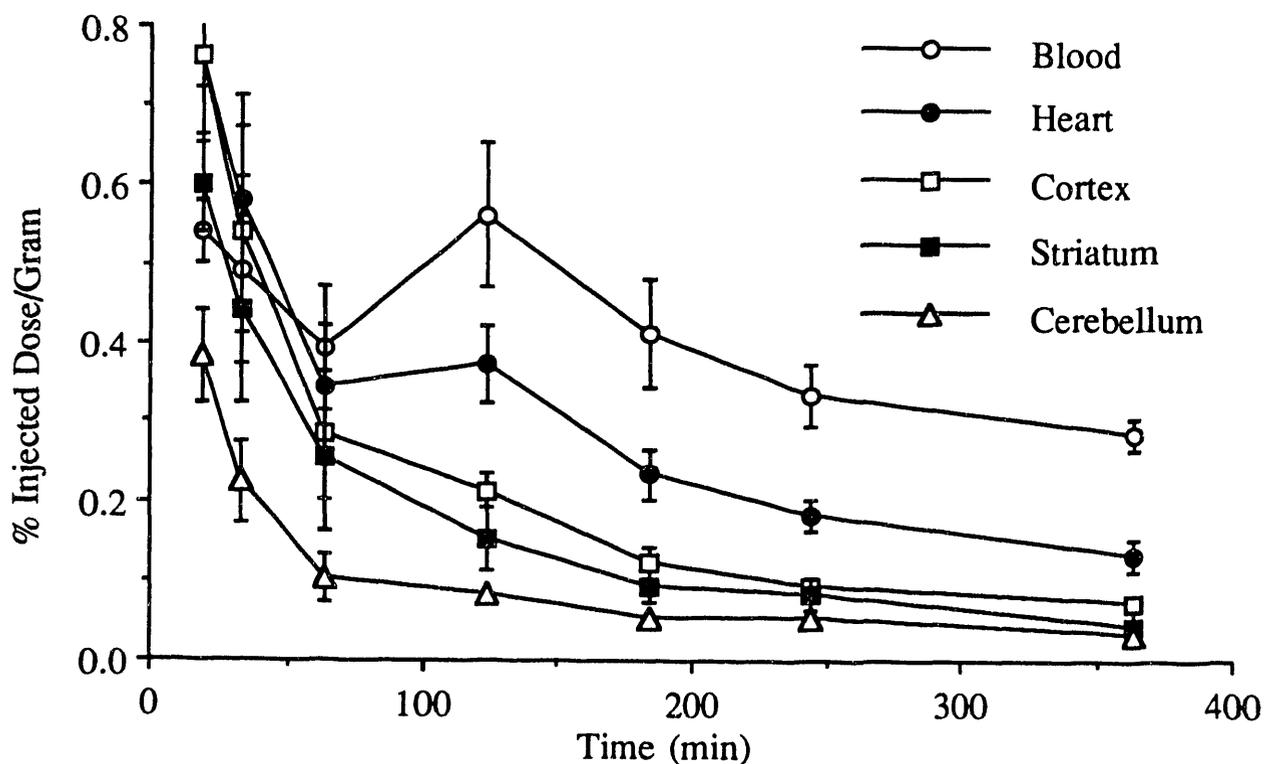


Figure 3. Biodistribution of "E,Z-1" in female rats.

Autoradiography of "E,Z-1" was performed by Dr. P. Som and co-workers at the Brookhaven National Laboratory and a typical ARG is shown in Figure 5. These studies were performed using [^{131}I]-"E,Z-1" and the slices obtained one hour post-injection. High uptake of activity was observed in the cortex, striatum, olfactory bulb, and hippocampus with very low uptake of activity in the cerebellum.

These combined results suggest that the E and Z configuration around the double bond may enhance the receptor subtype selectivity of IQNP (1). The uptake of "Z-1" is higher in these regions as compared to "E,Z-1" which contains only a small fraction of a Z isomer. We are currently separating the chiral centers of IQNP to obtain the best

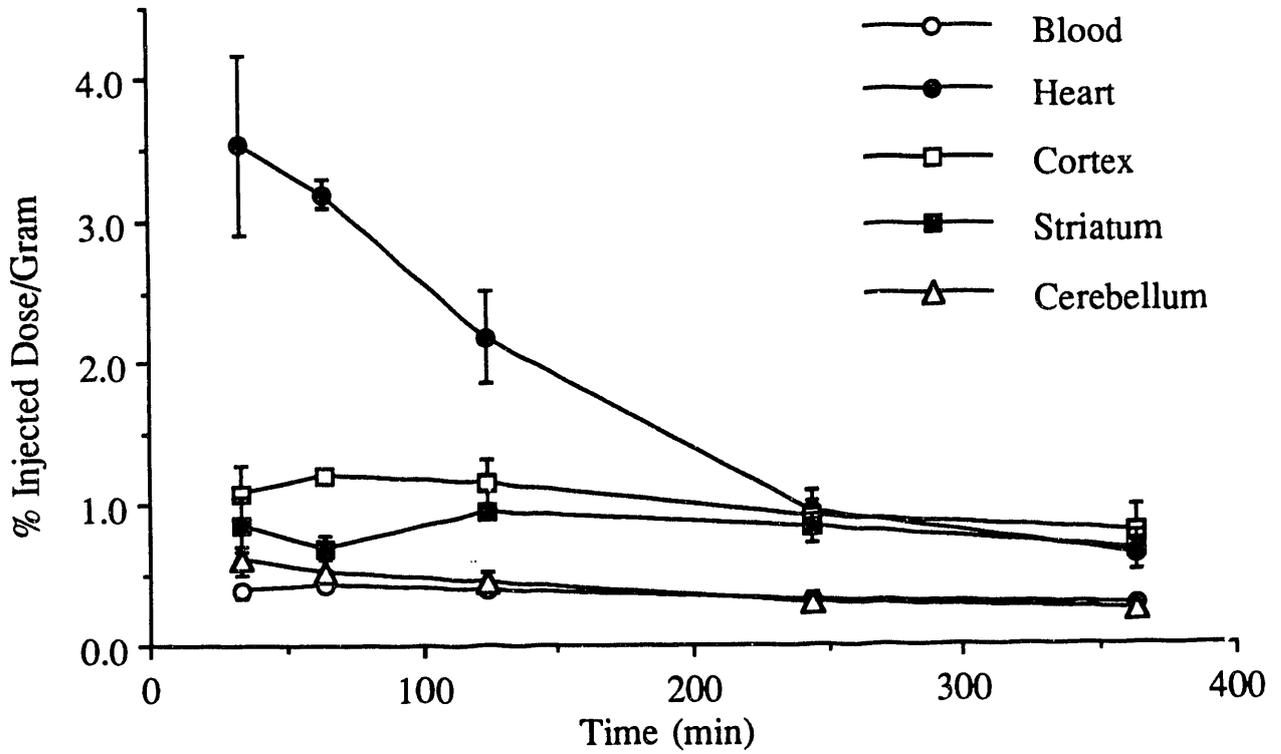


Figure 4. Biodistribution of "Z-1" in female rats.

candidates for future studies and to determine if a selective subtype isomer can be isolated.

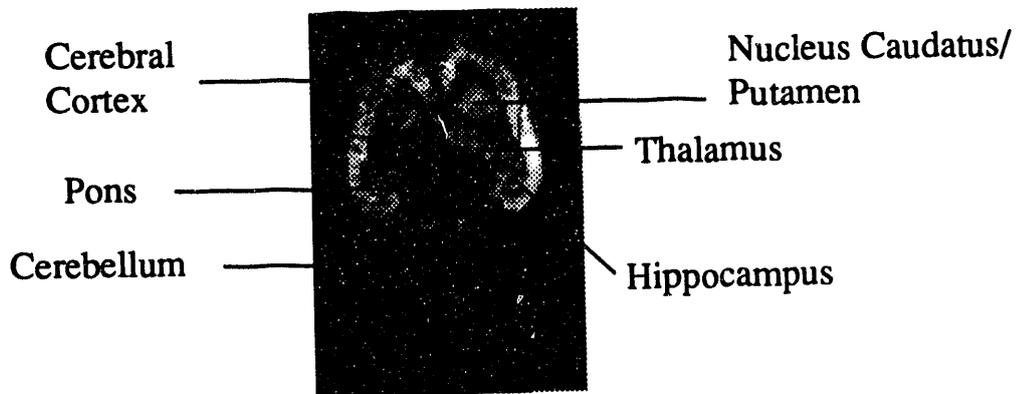


Figure 5. Autoradiographic studies of [¹³¹I]-E-Z-IQNP in rats.

DETERMINATION OF THERMAL AND EPITHERMAL NEUTRON FLUX VALUES IN HFIR HYDRAULIC TUBE POSITIONS

The shift from isotope production to material testing in the HFIR since restart of the HFIR in 1991 has perturbed the neutron fluxes and spectra. In addition, during the HFIR shut down, the hydraulic tube facility, which was originally located in the center of the flux trap, was relocated to an off-center position. For prediction of the production rates of radioisotopes of interest to us, it is very important to have an accurate knowledge of the neutron flux values of the hydraulic tube position, and a systematic "mapping" of the flux values was thus initiated. With the help of a summer student, a computer code was developed for the above purpose, and the thermal neutron fluxes were measured in all positions of the hydraulic tube (Figure 6.). A report is under preparation describing these activities. Currently with collaboration with two other divisions at ORNL, we are in the process of mapping the epithermal and fast neutron fluxes in the hydraulic tube.

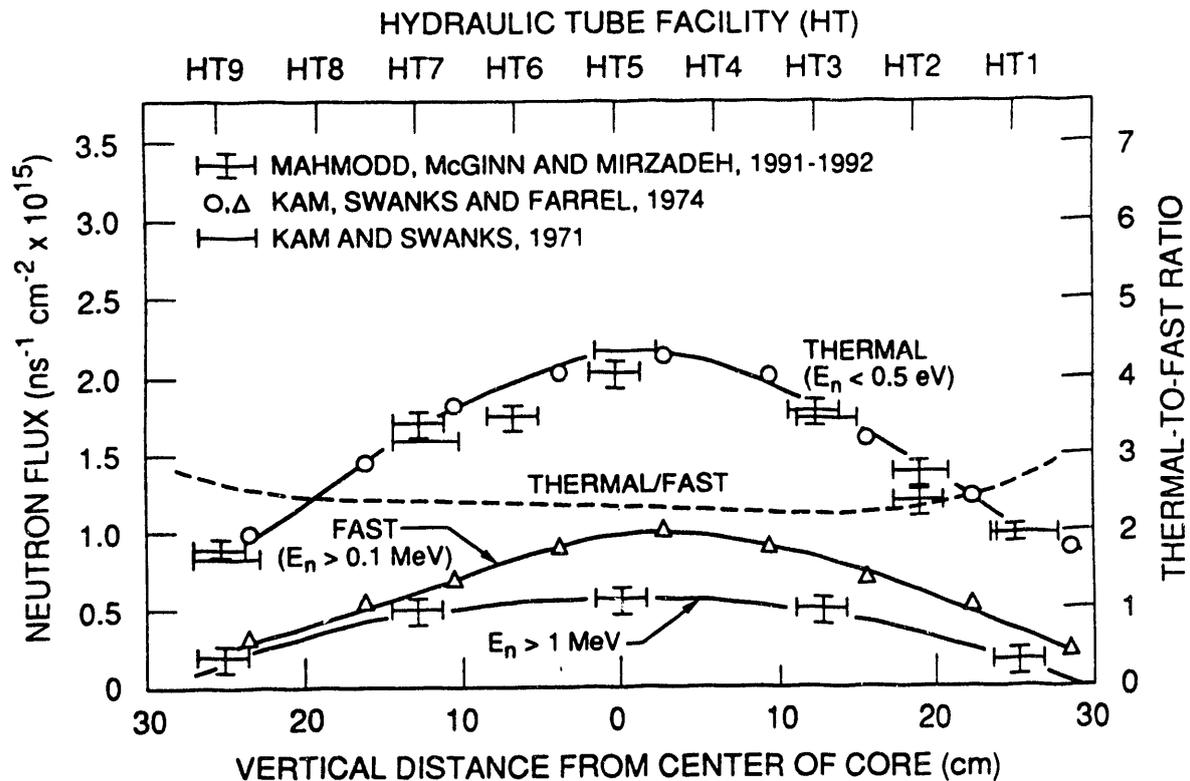


Figure 6. Neutron flux values measured in HFIR hydraulic tube positions

AGENTS FOR MEDICAL COOPERATIVES

In a continuation of collaborative studies to evaluate the regional uptake in cerebral structures by high resolution autoradiography (ARG), samples of I-125- and I-131-labeled "IQNP" were supplied to the Brookhaven National Laboratory (P. Som, D.V.M.). One of the ORNL tungsten-188/rhenium-188 generators was supplied for preclinical studies in a collaborative program with the University of Kent and Canterbury Hospital in England (P. J. Blower, Ph.D.).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

A new electrochemical technique has been developed to provide radioisotopes of copper for applications in nuclear medicine by the processing reactor-irradiated zinc targets. This technique represents an important improvement in providing carrier-free copper-67 for therapeutic applications and copper-64 for diagnostic use with positron emission tomography (PET).

Mirzadeh, S. and Knapp, Jr., F.F., "Spontaneous Electrochemical Separation of Carrier-Free Copper-64 and Copper-67 from Zinc Targets," *Radiochim. Acta*, 57, 193-199 (1992).

An "Editorial" was recently authored by F.F. (Russ) Knapp, Jr., S. Mirzadeh and A. P. Callahan, in a special issue of the journal, Radioactivity and Radiochemistry (Vol. 3, No. 4, 1992), which introduced sixteen papers from the "Symposium on Radionuclide Generator Systems for Nuclear Medicine Applications". The Symposium was organized by the ORNL researchers at the Annual Meeting of the American Chemical Society (ACS), held in Washington, D.C., on August 24-28, 1992. The symposium encompassed state of the art presentations on radionuclide generator systems for diagnostic and therapeutic applications in nuclear medicine.

Members of the ORNL Nuclear Medicine Group have published the first comprehensive overview summarizing the production capabilities of U.S. reactors for medical radioisotopes. The 190 page survey summarizes the production capabilities of nine U.S. reactors and will be an important resource for DOE staff, nuclear medicine researchers, and students.

S. Mirzadeh, R. E. Schenter, A. P. Callahan and F. F. (Russ) Knapp, Jr., "Production Capabilities in U.S. Nuclear Reactors for Medical Radioisotopes," ORNL/TM-12010.

Nuclear Medicine Group Technician Receives Certification

Carla Lambert, a Laboratory Technician in the Nuclear Medicine Group, has recently been certified as a Laboratory Animal Technician by the Animal Technician Certification Board of the American Association for Laboratory Animal Science (AALAS). This certification follows six months of preparatory course work, laboratory animal procedure training, laboratory exercises, and successful completion of the Laboratory Animal Technician examination. This is the first AALAS certification to be awarded to a member of Health and Safety Research Division and is an important accomplishment consistent with increased emphasis by federal agencies and by the ORNL Animal Care and Use Program on the training and certification of personnel involved with animal studies.

Presentation

Members of the ORNL Nuclear Medicine Group co-authored a recent paper describing the use of radioiodinated fatty acids for cardiac imaging to evaluate heart involvement in patients with myopathies of skeletal muscle which was presented at the *Annual Meeting of the American Heart Association*, held in New Orleans, Louisiana, on November 16-19, 1992. The collaborative studies were conducted by J. Kropp, M.D., and colleagues at the Clinic for Nuclear Medicine at the University of Bonn, Germany.

Kropp, J., Koehler, U., Zierz, S., Knapp, Jr., F.F., and Biersack, H.-J. "Radionuclide Imaging of Myocardial Oxidative Metabolism in Patients with Systemic Myopathies."

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