610

DEPARTMENT OF THE AIR FORCE
USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)
BROOKS AIR FORCE BASE, TEXAS 78235

11 FEB 1975

REPLY TO ATTN OF: RAH/I&RS Committee

SUBJECT: Application for Amendment to Radioactive Material Permit USAFSAM, Brooks AFB TX

TO: AMD/RDR

1. Attached is an application for amendment to USAFSAM Radioactive Material Permit No. 2-0015 which has been reviewed by the USAFSAM Isotopes and Radiation Sources Committee.

2. Request this application be reviewed and forwarded at the earliest possible time. Latest information from New England Nuclear Corporation indicates that Phase III testing will begin on or about 24 February 1975. In order to participate in the IND, USAFSAM should have approval for participation by this date. If approval is not granted in sufficient time, the possibility exists that New England Nuclear will not allow participation by USAFSAM.

EVAN R. GOLDRA, Colonel, USAF, MC
Commander

1 Atch
Application

AIR1.941130.066c

Atch 2

GTD

DEPARTMENT OF THE AIR FORCE
USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)
BROOKS AIR FORCE BASE, TEXAS 78235

REPLY TO ATTN OF: RAH/I&RS Committee

11 FEB 1975

SUBJECT: USAF Radioactive Material Permit No. 2-0015(C76)

TO: AFLC/SGPR

1. It is requested that USAF Radioactive Material Permit No. 2-0015(C76) issued to the USAF School of Aerospace Medicine, Brooks AFB, Texas be amended.

2. The following information is submitted in compliance with T.O. 00-110N-3:

a. Radioactive Material Required: Thallium-201 (^{201}Tl)* Sterile Solution as no-carrier-added Thallium chloride in 0.9% sodium chloride.

*Accelerator produced: Supplied by New England Nuclear Corporation, Atomlight Place, North Billerica MA 01862.

b. Name and Address:

Department of the Air Force
USAF School of Aerospace Medicine
Brooks AFB TX 78235

c. Base Accountability No.: FG3057

Same as above

d. Using Activity: Departments and physicians approved by the Isotopes and Radiation Sources Committee of applicant institution.

e. Individual Users: Isotopes and Radiation Sources Committee; same as application dated 21 Feb 1974. Primary Physicians: Colonel John H. Triebwasser and Major Thomas H. Loecker, experience and training (Atch 1).

f. Radiation Protection Officer: Mr. Robert E. Tatsch; same as application dated 21 Feb 1974.

g. Radiation Protection Program: Same as application dated 21 Feb 1974.

h. Dosimeters and Film Badge Service Available: Same as application dated 21 Feb 1974.

i. Equipment and Radiation Instrumentation: Same as application dated 21 Feb 1974.

j. Method, Frequency, and Standards Used in Calibrating Instruments: Same as application dated 21 Feb 1974.

k. Facilities and Equipment: Same as application dated 21 Feb 1974.

3. The USAF School of Aerospace Medicine (SAM) is the consultation center for the Continental United States for rated (flying) personnel whose physical condition has become suspect. Medical evaluations are conducted on these individuals to attempt to discern the cause of the physical disability.

a. Another function of the School is to determine the suitability of certain individuals for special projects, e.g., Apollo. These examinations are designed not only for the diagnosis of current medical maladies, but also to detect conditions which will adversely affect the individual's performance under stresses peculiar to the aerospace environment. Routine and some nonroutine diagnostic radioisotopic procedures are required as part of these examinations. Evaluations are carried out in the same manner on volunteer flyers and nonflyers in the investigation of effects of such stresses simulated in the laboratory. These stresses include weightlessness, hypoxia, hypobaric conditions, prolonged confinement, varying dietary intakes, vibration, and noise.

b. Clinical evaluations using radioisotopes will rarely be required more than twice on any individual. The whole body dose will be kept to a minimum in any consecutive 13 week period.

c. The most exacting up-to-date and reliable techniques are necessary to provide the best possible medical evaluation of each individual. At present, a number of routine and nonroutine procedures involving use of AEC licensed byproduct material are utilized in support of this School function.

d. The specific use of these radiopharmaceuticals is to provide noninvasive myocardial scintiphotos of aircrew members with suspected myocardial perfusion abnormalities. These will subsequently aid in determining candidates for cardiac catheterizations.

4. The proposal for use of this accelerator-produced radionuclide has been reviewed and approved by the School's Isotopes and Radiation Sources Committee.

a. The use of this radionuclide will be accomplished under a "Notice of Claimed Investigational Exemption for a New Drug" (IND) Phase III Protocol for Clinical Testing. The Phase III Protocol will be followed. The Protocols for Phases I and II are attached which give the pertinent information for evaluation of the procedure only. The School of Aerospace Medicine will participate only in the Phase III testing program expected to begin on or about 1 March 1975. A copy of the Phase III Protocol will be forwarded upon receipt from New England Nuclear Corporation.

b. The supplier will be requested to furnish USAF/SG with a statement confirming the existence of the IND and giving the School approval to investigate the new drug.

5. It is requested that this amendment be approved prior to receipt of Phase III Protocol to avoid any delays in beginning the clinical evaluations.

Robert E. Tatsch

ROBERT E. TATSCH
Radiation Protection Officer

2 Atch
1. Exp & Training
2. Protocol

Members of the Isotopes and Radiation Sources Committee

Colonel John H. Triebwasser, USAF, MC; Univ. of Missouri, 1951, M.D.; Internship, Wilford Hall USAF Hospital, 1962; Residency in Internal Medicine, Wilford Hall USAF Hospital, 1962-1965; Chief, Metabolic Function, Clinical Sciences Division, USAF School of Aerospace Medicine, Brooks AFB, Texas, June 1967-1971; University of Texas Medical School at Dallas, Texas, 1971-1973; Chief, Internal Medicine Branch, Clinical Sciences Division, USAF School of Aerospace Medicine, Brooks AFB, Texas, Aug 1973 - Present.

TRAINING AID EXPERIENCE

Type	Where Trained	Duration	OJT	Formal Course
a. Prin. of Radiation Protection	Wilford Hall USAF Hosp, Lackland AFB TX	5 yrs	Yes	No
b. Radioactivity Measurements & Monitoring	Same	5 yrs	Yes	No
c. Mathematical Calculations	Same	5 yrs	Yes	No
d. Biological Effects of Radiation	Same	5 yrs	Yes	No

EXPERIENCE WITH RADIATION

Isotope	Maximum Level	Where Handled	Duration	Type of Use
^{131}I	1-50 mci	Wilford Hall Hosp; USAF Hosp, Wright-Pat.	5 yrs	Diag. & Therapy
^{32}P	1-50 mci	Wilford Hall Hosp	3 yrs	Therapy
^{51}Cr	Sev. mci	Wilford Hall Hosp; USAF Hosp, Wright-Pat	5 yrs	Diagnosis
^{59}Fe	Sev. mci	Wilford Hall Hosp	2 yrs	Diagnosis
^{131}I	Sev. mci	Same	2 yrs	Diagnosis
[illegible]	1-50 mci	Same	2 yrs	Therapy
[illegible]	5 mci	UT Med School Dallas, Texas	2 yrs	Diagnosis

TRAINING AND EXPERIENCE

Major Thomas E. Loecker, USAF, MC; Creighton Univ, 1962, B.S.; Univ. of Nebraska Med. Sch., 1966, M.D.; St Mary's Hosp., 1966-1967, Internship; U.S.Navy, 1967-1970; St Mary's Hosp., 1970-1973, Residency Gen. Radiology; U.C.Davis at Sacramento Med. Cen., 1973-1974, Nucl. Med. Residency; 1974-Present, Chief, Radiology Function, Clinical Sciences Div, USAFSAM, Brooks AFB, Texas.

Type	Where Trained	Duration	OJT	Formal Course
a. Prin. of Rad. Protection	U.C.Davis, Sacramento Medical Center	1 yr	Yes	Yes
b. Radioactivity Measurement & Monitoring	Same	Same	Yes	Yes
c. Mathematical Calculations	Same	Same	Yes	Yes
d. Biol. Effects of Radiation	Same	Same	Yes	Yes

EXPERIENCE WITH RADIATION

Isotope	Maximum Level	Where Handled	Duration	Type of Use
Tc99m	400 mCi	U.Calif Davis	1 Yr	Diagnosis
Tc99m	10 mCi	Same	1 Yr	Diagnosis
I-131	100 uCi	Same	1 Yr	Therapy
I-131	200 uCi	Same	1 Yr	Diagnosis
I-131	300 uCi	Same	1 Yr	Diagnosis
In-111	500 uCi	Same	1 Yr	Diagnosis
Ga-67	1 mCi	Same	1 Yr	Diagnosis
RISA	1 mCi	Same	1 Yr	Diagnosis
Cr-51	1 mCi	Same	1 Yr	Diagnosis
P-32	1 mCi	Same	1 Yr	Diagnosis

EXPERIENCE WITH RADIATION
(Continued)

Isotope	Type of Use
Co-60 and 2 Mev Linear accelerator	Radiation Therapy for 9 months-Jul 71-Apr 72.
Strontium-90	External application
Radium implants	In tongue lesions and intracavitary radium for cervix lesions.
Orthovoltage X-ray Unit	Treatment of skin carcinomas.

NEW ENGLAND NUCLEAR

RADIOPHARMACEUTICAL DIVISION

INVESTIGATOR'S PROTOCOL:
PHASE I AND II STUDY OF THALLIUM CHLORIDE Tl 201 FOR MYOCARDIAL IMAGING IN ACUTE INFARCTION AND/OR ISCHAEMIA

The data submitted by you will be used by New England Nuclear Corp. in preparing and filing a New Drug Application (NDA) with the Food and Drug Administration (FDA). Therefore, the purpose of the program is to objectively demonstrate to the FDA the diagnostic utility and safety of the NEN Thallium Chloride Tl 201 for myocardial imaging. This radiopharmaceutical is currently distributed as an investigational new drug.

NEN THALLIUM CHLORIDE Tl 201

NEN Thallium Chloride Tl 201 is supplied in isotonic solution as a sterile non-pyrogenic radiopharmaceutical for intravenous injection as a myocardial imaging agent. The aqueous solution contains 1 mCi Thallium Chloride Tl 201 per milliliter adjusted to pH 4.5 - 8.0.

Complete product information is contained in the package insert accompanying each vial, a copy of which is attached. The study is subject to the warnings and precautions noted in the package insert.

FORM FD-1572

This study is also subject to the conditions described in Food and Drug Administration Form FD-1572. These regulations provide that each investigator submit an executed copy of this form, together with his curriculum vitae, to New England Nuclear, Radiopharmaceutical Division, Atomlight Place, North Billerica, Massachusetts 01862.

PATIENT SELECTION

The patients to be included in this study will be those who have been referred to the nuclear medicine department of each participating institution for the evaluation of a clinically demonstrated or suspected myocardial infarction and/or ischaemia. Patient with suspected infarction should have imaging performed as soon after the event as possible. During the term of the study all patients referred for

imaging and accepted for the evaluation of myocardial infarction and/or ischaemia must be included in the study. Patient may be of either sex and of varying ages above 18. Pregnant and lactating women and children under 18 should undergo this procedure only if, in the judgement of the responsible physician, the potential benefits outweigh the risks.

NUMBER OF PATIENTS

A minimum of 5 patients per investigator. All studies related to myocardial infarction and/or ischaemia performed by a given investigator during the period of this study must be included in the tabulation of the case reports.

PATIENT CONSENT

Informed consent will be obtained from each patient for the use of this investigational new drug in accordance with the requirements of Form FD-1572, Section 6g. Each investigator will forward to NEN a copy of the form used at his institution.

METHODS

The recommended dose of Thallium Chloride Tl 201 is 1-2 mCi per patient. The desired dosage is measured by a suitable radioactivity calibration system and is injected intravenously.

After a predetermined interval imaging is performed using a rectilinear scanner or a gamma camera. All procedures must, of course, be performed by appropriately skilled and licensed physicians or technicians with primary regard for patient safety.

In dealing with patients in whom myocardial infarction or ischaemia is known or suspected, extreme care must be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedures.

ADVERSE REACTIONS

All patients should be under the observation of the nuclear medicine departments as well as the cardiology service during the time of the imaging procedure in accordance with good clinical pratic Any adverse effects observed during the period of patient observation should be treated and recorded in detail. Particular care should be taken to determine whether the adverse reactions were related to the imaging agent.

In the unlikely event of a severe adverse drug reaction related to the use of Thallium Chloride Tl-2
please contact NEN immediately at (617) 667-9531, ext. 395.

EVALUATION

The participating investigators will evaluate the imaging agent by noting its biological distribution and the quality of the pictorial image it produces. In accordance with good clinical practice, site of abnormal uptake will be noted. The final clinical impression will be based on the interpretation of the image along with a consideration of other available clinical data. For the purpose of this st a case report form will be completed on each patient noting the above information along with certa correlative clinical data that will allow comparison of the results of imaging data with information gained using other procedures.

Instructions for the completion of the case report forms are attached.

THALLIUM CHLORIDE Tl 201 FOR MYOCARDIAL IMAGING

NAME

Thallium Chloride Tl 201, as the chloride, for intravenous administration.

DESCRIPTION

Thallium Chloride Tl 201 is supplied in isotonic solution as a sterile, non-pyrogenic radiopharmaceutical. The aqueous solution at calibration time contains 1 mCi/ml of Thallium 201, adjusted to pH 4.5 - 8.0, 0.9% sodium chloride, and 0.9% benzyl alcohol as a preservative. It is carrier-free with less than .2% Pb 203 and 1.5% Tl 202.

ACTIONS

Biologically, the distribution of thallous ion (Tl^+) following intravenous administration has been shown to be similar to potassium ion (K^+). Its disappearance from plasma, its uptake and concentration in tissues, and its routes of excretion also seem to be analogous to those of potassium. For example, Hollins and Moore (1), in their study of the movement of thallium ion in frog muscle concluded that the sartorius muscle fiber cannot distinguish between Tl^+ and K^+ when the concentration of thallium is kept low. This suggests that the uptake of Tl^+ by human heart muscle should be very similar to that of K^+.

Recently, Bradley-Moore, et al (2) found that in normal goats, the maximum myocardial concentration, 3.7% of the injected dose of Thallium 201 was attained in 10-25 minutes and remained high for at least 2 hours. The relative concentration with respect to neighboring organs, such as liver and lung is optimal between 10 and 25 minutes post injection.

INDICATIONS

Thallium Chloride Tl 201 is indicated for myocardial imaging in acute infarction and/or ischaemia.

CONTRAINDICATIONS

There are no known contraindications to the use of Thallium Chloride Tl 201.

WARNINGS

This radiopharmaceutical preparation should not be administered to pregnant or lactating women, or persons under the age of 18, unless the benefits to be gained outweigh the potential hazards.

Patients in coronary care units undergoing tests for acute myocardial infarction should be carefully monitored.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by a nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

PRECAUTIONS

In the use of any radiopharmaceutical, care should be taken to insure minimal radiation exposure to the patient as well as to personnel involved in the procedure, by using the smallest dose of radioactivity consistent with safety and the relative value of the diagnostic information.

ADVERSE REACTIONS

No adverse reactions based on the use of this agent in the literature to date have been reported.

PHYSICAL CHARACTERISTICS

Thallium Chloride Tl 201 with a physical half-life of 73.5 hours decays by electron capture to Mercury 201.

Table I. Principal Radiation Emission Data

Radiation	Mean %/Disintegration	Mean Energy (keV)
γ_4	2%	135
γ_6	8%	168
Mercury X-Rays	93%	69-80

The specific gamma ray constant for Tl 201 is 0.42R/mCi-hr. at 1 cm. The half-value layer is 0.35 mm of lead. Note that the use of a 4 mm thickness of lead will attenuate the radiation exposure from millicurie amounts of Thallium 201 by a factor of about 10,000.

DOSIMETRY

Thallium 201	Rads/mCi
Heart	.19
Kidneys	2.1
Liver	0.27
Gonads	0.34

THALLIUM TI 201 DECAY CHART Half-Life 73 Hours			
Hours	Fraction Remaining	Hours	Fraction Remaining
-72	1.98	42	0.67
-60	1.77	48	0.63
-48	1.58	54	0.60
-36	1.41	60	0.57
-12	1.12	66	0.53
- 6	1.06	72	0.50
0*	1.00	78	0.48
6	0.94	84	0.45
12	0.89	90	0.43
18	0.84	96	0.40
24	0.80	108	0.36
30	0.75	120	0.32
36	0.71	132	0.29
		144	0.25

*Calibration Time

DOSAGE AND ADMINISTRATION

The recommended dose of Thallium Chloride TI 201 is 1-2 mCi administered intravenously. Imaging may commence immediately after dose. Higher dosage or slightly longer imaging time may be required when cardiac gating is employed.

HOW SUPPLIED

Thallium Chloride TI 201 injection is supplied as a sterile, non-pyrogenic solution containing at calibration time 1 mCi/ml of Thallium TI 201, 9 mg/ml sodium chloride, and 9 mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-8.0 with either hydrochloric acid or sodium hydroxide solutions.

TOXICITY

Literature reports of the acute toxicity of thallium in man and animals, as well as tests conducted at NEN in mice indicate that the maximum diagnostic dose (2 mCi) of Thallium Chloride Tl 201 (10 nanograms) has an enormous margin of safety.

Bradley and Moore, et al (2) observed no toxicity in 14 goats and two dogs given up to 7 micrograms of stable thallium. One goat was injected with 1000 micrograms of thallium with no untoward effect.

REFERENCES

1. Mullins, L.J. and Moore, R.D. The Movement of Thallium Ions in Muscle. J. Gen. Physiol. 43:759-73 (1960).
2. Bradley-Moore, P., Lebowitz, E., Greene, M. et al. Thallium 201 for Medical Use II Biological Behavior - Personal Communication to New England Nuclear.
3. Rusznyak, I., Gyorgy, H., Porter, J. et al. On Some Potassium-Like Qualities of the Thallium Ion. Experimentia 24:809-10 (1968).
4. Lebowitz, E., Green, M.W., Bradley-Moore, P. et al. ^{201}Tl for Medical Use. J. Nucl. Med. 14:421-2 (1973).
5. Hurley, P.J., Cooper, M., Reba, R.C. et al. ^{43}KCl: A New Radiopharmaceutical for Imaging the Heart. J. Nucl. Med. 12:516-519 (1971).
6. Strauss, H.W., Zaret, B.L., Martin, N.D. et al Noninvasive Evaluation of Regional Myocardial Perfusion with Potassium-43. Radiology 108:85-90 (1973).
7. Lebowitz, E., Greene, M.W., Bradley-Moore, P. et al. Thallium 201, Personal Communication to New England Nuclear.
8. Kawana, M., Drizek, H., Porter, J. et al. Use of ^{199}Tl as a Potassium Analog in Scanning. J. Nucl. Med. 11:333 (1970).

INSTRUCTIONS FOR COMPLETING CASE REPORT FORM FOR EVALUATION OF NEN THALLIUM CHLORIDE TI 201 FOR MYOCARDIAL IMAGING IN ACUTE INFARCTION AND/OR ISCHAEMIA

The data from this study will be used by New England Nuclear Corp. to prepare and file a New Drug Application (NDA) with the Food and Drug Administration (FDA). It is essential that case report forms be filled for all patients undergoing myocardial imaging with the NEN Thallium Chloride TI 201 during the period of this study.

In order to evaluate the results from several centers, all participating clinicians must follow the same protocol and use identical case report forms. It is extremely important that the case report form be completely filled out. In the rare situation where some data may not be available, please indicate why that data was omitted.

To assist you in providing the necessary data, we have organized the case report form into the following sections:

Index Information

A. Patient Information
B. Dosage Information
C. Adverse Effects
D. Image Findings
E. Correlation to Other Clinical Procedures
F. Evaluation

Specific instructions follow below:

Index Information

Case Number - Indicate the sequential number of the imaging procedure on this study series.

Referring Physician - Indicate the patient's own physician for possible future reference.

Date of Scan - Date imaging procedure performed.

NEN Drug Lot Number - The lot number printed by NEN on the label of the thallium vial.

Patient Information

1. Patient's Initials, Hospital Number, Age, Sex and Weight – as obtained from patient interview or from the patient's record.
2. Clinical Presentation – briefly list the referring physician's description of the patient's history, symptoms and signs related to the image request. Indicate the type of tests used to establish the pre-imaging probable diagnosis and those test results.
3. Probable Diagnosis – what is the referring physician's initial diagnosis at the time he requested the imaging procedure.
4. Indications for Imaging – why was the procedure requested, i.e., to visualize a pathologic lesi to rule out the presence of a disease state, to gauge the patient's response to therapy or to follow the course of a disease.
5. Patient Consent – the informed consent of each patient must be obtained for the use of this investigational new drug. The physician completing this form must initial this section (1) to certify such consent has been obtained in accordance with the requirements of Form 1573, Section 4g, and (2) to validate the form in accordance with FDA regulations.

Dosage Information

1. Intravenous Dose – please indicate the dose of imaging agent actually administered to the patie in terms of both total millicuries and μCi/kg body weight.
2. Interval in minutes between intravenous injection of the imaging agent and the imaging procedu
3. Estimated interval in hours infarct, if any, and imaging procedure.
4. Indicate the imaging equipment used in the procedure
5. Explain any image enhancement technique that may have been used prior to interpretation.

Adverse Effects

Indicate whether any adverse drug response was observed during the use of the NEN Thallium Chlori Tl 201. If yes, please describe the incident fully on a separate sheet and indicate whether the reaction was considered related to the administration of the imaging agent.

In the unlikely event of a severe adverse drug reaction, please contact NEN immediate at (213) 667-9531, ext. 305.

THE REPORT FORM ARE CRITICAL AND ALL INFORMATION REQUESTED NEEDED FOR PROPER EVALUATION. OF PARTICULAR IMPORTANCE IN ESTABLISHING THE VALUE OF THIS DIAGNOSTIC AGENT IS:

i. A COPY OF YOUR REPORT AS SUBMITTED TO THE REFERRING PHYSICIAN

ii. THE RESULTS OF CORRELATIVE CLINICAL PROCEDURES

iii. THE FINAL PATIENT DIAGNOSIS

D. Image Findings

1. Image Quality - provide your evaluation of the image quality in terms of its being acceptable or unacceptable for interpretation. If unacceptable, it is extremely important to explain the reasons.
2. Agent Distribution - state whether the distribution (uptake) of the agent in the patient's myocardium is, in your opinion, normal or abnormal.
3. Sites of Abnormal Uptake - please describe in terms of anatomical location. This will aid in evaluating uptake specificity and efficacy in terms of regional location and will help in interpreting the correlative data.
4. Clinical Interpretation (Impression) - a copy of your report to the referring physician should be attached. Please delete the patient's name and provide patient's initials. If impossible to provide copy of report please review your impression based on the imaging procedure.

E. Correlation to Other Procedures

1. In this section please check the box indicating the results of the other listed procedures bearing on the specific lesion indicated by imaging. List the results of these procedures reflecting known or suspected myocardial infarction and/or ischaemia which may not have been visualized by the imaging.
2. Indicate whether, in your judgement, the imaging procedure was of value or was not of value to the patient. Please explain the basis for this judgement.
3. Indicate the patient's final diagnosis as determined by the referring physician.

evaluation

Considering all of the above information, indicate whether the agent was of value in the diagnosis or clinical management of the patient. Please explain your reply and place any other evaluative remarks in the space provided.

IN ORDER FOR THE CASE REPORT FORM TO BE COMPLETE AND ACCEPTABLE TO THE FDA, THE INVESTIGATOR MUST SIGN THE FORM AT THE CONCLUSION OF THE REPORT ALONG WITH THE DATE AND COMPLETE ADDRESS OF THE INSTITUTION.

Thank you again for your interest and cooperation in this effort.

CLINICAL CASE REPORT FORM

THALLIUM CHLORIDE Tl 201 FOR MYOCARDIAL IMAGING

Case No.: _____ Date of Scan: _____

Referring Physician: _____ NEN Drug Lot No.: _____

A. PATIENT INFORMATION

1. Patient's Initials: _____ Hospital No.: _____ Age: _____ Sex: _____ Weight: _____
2. Clinical Presentation (History, Symptoms, Signs): _____
3. Probable Diagnosis: _____
4. Indication(s) (Reasons) For Imaging: _____
5. Patient Consent: Patient has been advised that an investigational drug is to be administered and has consented to its use. Physician's Initials: _____

B. RADIOISOTOPE INFORMATION

1. Intravenous Dose _____ mCi _____ µCi/kg Body Weight
2. Interval Between Dose Administration and Imaging _____ Minutes.
3. Estimated Interval Between Infarct, if any, and Imaging Procedure _____ Hours.
4. Imaging was performed using a: ☐ rectilinear scanner ☐ gamma camera ☐ other: _____
5. Was any technique used to alter the imaging output prior to interpretation? ☐ No ☐ Yes
   Please Explain: _____

C. ADVERSE EFFECTS

1. Were Any Adverse* Patient Responses to Thallium Chloride Tl 201 Observed? ☐ No ☐ Yes
   *In the unlikely event of a severe adverse drug reaction, please contact NEN immediately at (617)657-9531, x305.
2. If Yes, Identify Effect and Detail Treatment--Attach Separate Report. _____
3. Do You Consider the Effect Related to the Drug? ☐ No ☐ Yes Explain: _____

IMAGE FINDINGS

1. Image Quality: ☐ Acceptable ☐ Unacceptable If Unacceptable, Comment (Describe):

2. Agent Distribution: ☐ Normal ☐ Abnormal

3. Site(s) of Abnormal Uptake:

4. Clinical Interpretation (Impression): (attach copy of report to referring physician)

E. CORRELATION TO OTHER PROCEDURES

1. Relate Image Interpretation to Results of Other Procedures

data not done	PROCEDURES	date performed	consistent	inconsistent	FINDINGS
☐ ☐	EKG		☐	☐	
☐ ☐	Enzymes:		☐	☐	
☐ ☐	Vector Cardiogram		☐	☐	
☐ ☐	Cardiac Angiography		☐	☐	
☐ ☐	Exercise Testing		☐	☐	
☐ ☐	Other Radionuclide Agent Specify:		☐	☐	
☐ ☐	Other Procedure Specify:		☐	☐	
☐ ☐	Autopsy		☐	☐	

2. Did Imaging Information Contribute to Patient Diagnosis and/or Management? ☐ Yes ☐ N

Please Explain:

3. Patient Diagnosis:

EVALUATION

The Imaging Agent ☐ Was ☐ Was Not Considered to be Clinically Useful for this Patient.

Comments:

Signature Date Address (Institution)

NEN THALLIUM CHLORIDE TI 201 FOR MYOCARDIAL IMAGING

PROTOCOL FOR CLINICAL SAFETY TESTING: PHASE I & II

The evaluation of safety of NEN Thallium Chloride TI 201 will involve the following studies:

A. Observation for adverse reactions on hospitalized patients for 48 hours post-injection.

B. Measurement of vital signs for 24 hours post-injection.

C. Blood and urine measurements

D. Urinary excretion data

E. Blood distribution studies

A. Adverse Reactions:

All patients in the Phase I and II stage of investigation will be selected from the in-patient population of the participating hospitals to assure close, continuous follow-up.

Patients undergoing myocardial imaging with this agent will be under the observation of their attending physician or the nuclear medicine department physician for 48 hours after imaging for possible adverse effects.

In dealing with patients in whom myocardial infarction or ischaemia is known or suspected, extreme care will be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedures. All such patients will be under the observations of the cardiology service as well as the nuclear medicine department during the imaging procedure.

Most particularly, the patients will be observed by the nuclear medicine department for one hour post-injection for signs of adverse reactions. In addition, the patient's medical records will be reviewed by the investigator for any other indication of adverse reactions after at least 48 hours have elapsed post-injection.

If any adverse reaction is recorded, the investigator should, of course, immediately institute appropriate clinical support procedures and notify New England Nuclear at (617) 667-9531, x3
Any remaining portion of the imaging agent should be retained and returned to New England Nuclear, Radiopharmaceutical Division, Atomlight Place, North Billerica, Mass. 01862 by registered mail for further study.

Case No.: _____ Form A

NEN THALLIUM CHLORIDE TI 201 FOR MYOCARDIAL IMAGING

Phase I and II Safety Evaluation

ADVERSE REACTION

Date of Scan: _____

NEN Drug Lot No.: _____

Patient's Initials: _____ Hospital No.: _____ Age: _____ Sex: _____ Weight: _____

Probable Diagnosis: _____

_____

_____

Intravenous Dose: _____ mCi _____ ml

Was Any Adverse Reaction to the Imaging Agent Observed? ☐ Yes ☐ No

Specifically, Were Any of the Following Sequelae to the Imaging Procedure Observed?

Hemodynamic	☐ Yes	☐ No	Neurologic	☐ Yes	☐ N
Allergic	☐ Yes	☐ No	Dermatologic	☐ Yes	☐ N
Febrile	☐ Yes	☐ No	Respiratory	☐ Yes	☐ N

Other: _____

If the Answer to Any of the Above Questions is Yes, Please Complete the Following Section Completely:

Indicate the Time Post-Injection: _____

Existing or Prior Disorders: _____

_____

Past Drug Reactions or Allergic History: _____

_____

Was There Previous Exposure to This Imaging Agent? ☐ Yes ☐ No Date: _____

Describe reaction fully (include appropriate lab tests and patient vital signs): _____

_____

_____

_____

Treatment:

Patient Response:

In Your Opinion, Was the Reaction Related to the Injection of the Imaging Agent? ☐ Yes ☐

If Yes, Why; If No, Why Not:

B. Vital Signs:

Vital signs (blood pressure, pulse, respiration, temperature) will be taken on all patients immediately before injection and at specified times post-injection:

1 Hour
8 Hours
16 Hours
24 Hours

Pre-injection and one hour control data will be obtained on patients receiving a somewhat comparable agent, i.e., K-43, Tc 99m Glucoheptonate, Tc 99m HSA. It is understood that patients with myocardial infarction are often extremely ill and show unstable vital signs. Thus a further control group of patients in whom no imaging procedure is performed will have vital signs recorded for comparison.

Two to four investigators will each evaluate at least ten patients in this manner.

Case No.: _____ Form B

NEN THALLIUM CHLORIDE TI 201 FOR MYOCARDIAL IMAGING

Phase I and II Safety Evaluation

Date of Scan: _____

NEN Drug Lot No.: _____

Patients Initials: _____ Hospital No.: _____ Age: _____ Sex: _____ Weight: _____

VITAL SIGNS:

	Pre-Injection	1 Hour	8 Hours	16 Hours	24 H
Temperature					
Pulse					
Respiration					
Blood Pressure					

C. Blood and Urine Measurements:

To evaluate the possibility of any unrecognized effects of the agent, routine urinalyses will be obtained pre-injection and at 24-48 hours post-injection.

Determinations of serum BUN and SGOT and complete blood counts will also be obtained pre-injection and 24 hours post-injection.

Appropriate controls will be carried out using patients with comparable pre-existing clinical diagnoses.

Two to four investigators will each evaluate at least five patients in this manner.

Case No.: Form C

NEN THALLIUM CHLORIDE TI 201 FOR MYOCARDIAL IMAGING

Laboratory Data

Patient's Initials: Hospital No.: Date of Scan: NEN Drug Lot No.:

	Pre-Injection	24-48 Hours Post-Injectio
CBC:	Date:	Date:
Hemoglobin		
Hematocrit		
White Blood Cell Count		
Polys		
Bands		
Lymphs		
Monos		
Eos.		
Basos.		
Other		
URINALYSIS:	Date:	Date:
Sp. Gravity		
pH		
Protein		
Hemoglobin		
Glucose		
Ketones		
Sediment		
wbc		
rbc		
casts		
BLOOD:	Date:	Date:
BUN		
SGOT		

Physician's Signature:

D. Urinary Excretion Rate:

The urinary excretion rate of the radioactive label will be determined by performing several 24 hour urine collections from hospitalized patients who have received NEN Thallium 201 for myocardial imaging.

The 24 hour urine samples will be collected for three consecutive periods post-injection:

0-24 Hours
24-48 Hours
48-72 Hours

The volume of the sample will be recorded and an aliquot counted to determine thallium excretion.

Two investigators will each evaluate at least five patients in this manner.

Case No.: _____ Form D

NEN THALLIUM CHLORIDE TI 201 FOR MYOCARDIAL IMAGING

Phase I and II Safety Evaluation

Date of Scan: _____

NEN Drug Lot No.: _____

Patient's Initials: _____ Hospital No.: _____ Age: _____ Sex: _____ Weight: _____

EXCRETION OF INJECTED DOSE

24 Hour Urine Samples

Time After Injection:	CPM*	% Injected Dose
0 - 24 hrs	_____	_____
24 - 48 hrs	_____	_____
48 - 72 hrs	_____	_____

*Corrected for Physical Decay

E. Blood Distribution:

The blood distribution of the injected agent will be determined at specific intervals post-injection.

Aliquots of whole blood will be collected at specified intervals and their radioactivity measured. These studies will be done at the following times post-injection:

15 minutes
1 Hour
4 Hours
24 Hours
48 Hours

Two investigators will each evaluate at least five patients in this manner.

Case No.: _____ Form E

NEN THALLIUM CHLORIDE Tl 201 FOR MYOCARDIAL IMAGING

Phase I and II Safety Evaluation

Date of Scan: _____

NEN Drug Lot No. _____

Patient's Initials: _____ Hospital No.: _____ Age: _____ Sex: _____ Weight: _____

DISTRIBUTION OF INJECTED DOSE

Time After Injection:	Whole Blood CPM*/ml
15 Min.	_____
1 Hr.	_____
4 Hrs.	_____
24 Hrs.	_____
48 Hrs.	_____

*Corrected for physical decay.

Biodistribution:

$$T_{eff} = \frac{T_b \times T_{phys}}{T_b + T_{phys}}$$

where: T_b = Biological Half-Life

T_{phys} = Physical Half-Life

T_{eff} = Effective Half-Life

The physical half-life of Tl 201 is 73.5 hours.

Based upon animal studies and assuming instantaneous uptake, the effective half-times are:

Heart	0.8% has T_b = 1.8 hr.	$\therefore T_{eff}$ = 1.8 hr.
	0.45% has T_b which is very long and	$\therefore T_{eff} \cong T_{phys}$ = 73.5 hrs.
Liver	1.9% has T_b = 2.3 hr.	$\therefore T_{eff}$ = 2.2 hr.
	3% has T_b which is very long and	$\therefore T_{eff} \cong T_{phys}$ = 73.5 hrs.
Kidneys	11% has T_b which is very long and	$\therefore T_{eff} \cong T_{phys}$ = 73.5 hrs.

Equations:

The primary equation for calculating radiation dose is listed below:

$$D = \frac{\tilde{A}}{m} \sum \Delta_i \phi_i$$

where: $\tilde{A}$ = the cumulative activity of the source in μCi-hrs.

m = mass of target organ in gm.

Δ_i = equilibrium dose constant for the radiation of type i in gm-rad/μCi-hrs.

ϕ_i = absorbed fraction for the i^{th} type of radiation.

D = radiation dose in rads.

Cumulative Activity:

$$\tilde{A} = 1.44\,(1000)\,\frac{(\%\ \text{source organ uptake})}{100}\,(T_{eff})\ \mu\text{Ci-hr}$$

Calculations:

Using the biodistribution data noted above, the following cumulative activity ($\tilde{A}$) calculations were made: assuming a 1 mCi administered dose

Heart

$$A_1 = 1.44\,(1000)(.008)(1.8) = 20\ \mu\text{Ci-hrs}$$
$$A_2 = 1.44\,(1000)(.0045)(73.5) = 480\ \mu\text{Ci-hrs}$$
$$A = A_1 + A_2 = 500\ \mu\text{Ci-hr}$$

Liver

$$A_1 = 1.44\,(1000)(.019)(2.2) = 60\ \mu\text{Ci-hrs}$$
$$A_2 = 1.44\,(1000)(.031)(73.5) = 3281\ \mu\text{Ci-hrs}$$
$$A = A_1 + A_2 = 3341\ \mu\text{Ci-hr}$$

Kidney

$$A = 1.44\,(1000)(.055)(73.5) = 5821\ \mu\text{Ci-hr}$$

Radiation Emission Data:

The energies used in the following dosimetry calculations are:[1]

Radiation (i)	MeV	Δ_i
Gamma-4	0.135	0.0074
Gamma-6	0.168	0.030
Kα-1 X-Ray	0.071	0.070
Kα-2 X-Ray	0.069	0.038
Kβ-1 X-Ray	0.080	0.020
Non-Penetrating		0.091

[1] Any radiation (i) with an equilibrium dose constant (Δ_i) less than 0.010 g.-rad/μCi-hr was not considered.

Dose to Heart:

Heart Mass = 600 gm

The dose to the heart consists of the self-dose[1] and the dose from the kidney and liver.

$$D = \frac{500}{600}\,[0.216] + \frac{5821}{600}\,[0.0078] + \frac{3341}{600}\,[0.0016]$$

$$= 0.18 + 0.004 + 0.009$$

$$= 0.19 \text{ Rads}$$

Dose to Kidney:

Kidney Mass = 300 gm

The dose to the kidney consists of the self-dose and dose from liver.

$$D = \frac{5821}{300}\,[0.108] + \frac{3341}{300}\,[0.001]$$

$$= 2.10 + 0.011$$

$$= 2.1 \text{ Rads}$$

Dose to Liver:

Liver Mass = 1800 gm

The dose to the liver consists of the self-dose and dose from the kidney.

$$D = \frac{3341}{1800}\,[0.13] + \frac{5821}{1800}\,[0.005]$$

$$= 0.25 + 0.02$$

$$= 0.27 \text{ Rads}$$

Dose to Gonads[2]:

Gonad Mass = 70,000 gm

Conservatively, we assume that 100% of the injected dose goes to the total body and that there is no biological clearance.

$$A = 1.44 \times 1000 \times 73.5 = 105{,}840\,\mu\text{Ci-hr}$$

$$D = \frac{105{,}840}{70{,}000}\,(0.23)$$

$$= 0.34 \text{ Rads}$$

(1) Values for heart to heart were calculated by Walter S. Snyder of Oak Ridge.

(2) Assumed to be an absorbed fraction for a central point source in an elliptical cylinder or ellipsoid.

C. Toxicity

1. Introduction

The toxicity of any substance in a living organism can only be meaningfully discussed in relation to its dose. For virtually any toxic material, there exists a "no effect level", i.e., limiting dose below which there is no detectable pharmacological response in the organism. The millicurie quantities of carrier free isotope administered to patients in diagnostic procedures constitute such vanishingly small quantities of material that, in most cases, these doses are several orders of magnitude below the no effect level.

2. Human Dose

The weight of thallium corresponding to 1 mCi of carrier free ^{201}Tl may be calculated as follows:

since: $W = CNMT_{\frac{1}{2}}$

where: W = weight of isotope in μg

C = constant = 3.19×10^{-10}

N = number of μCi

M = atomic weight = 201

$T_{\frac{1}{2}}$ = half-life in hours = 73.5

then: $W = (3.19 \times 10^{-10})\ (1000)\ (201)\ (73.5)$

$= 4.7 \times 10^{-3}\ \mu g/mCi$

This means that each mCi of ^{201}Tl corresponds to less than 5 nanograms of material. Since the maximum recommended human dose of ^{201}Tl for myocardial imaging is

2.0 mCi, the diagnostic dose in a 70 kg man is 0.13 nanograms/kg.

3. Toxicity Literature

Knowledge of the pathophysiological effects of thallium in humans comes from early clinical use of thallium salts as depilatories and from cases of accidental suicidal, and criminal poisoning. Currently thallium containing compounds are still in limited use as rodenticides.

Following oral or parenteral administration thallous salts are rapidly absorbed and fairly equally distributed over all parts of the body. Higher concentrations are found in scalp hair, kidneys, and heart muscle, while nerve and fatty tissues show almost no accumulation (1, 2, 15, 16). In general, the distribution of Tl^+ is similar to K^+ with a higher concentration of Tl^+ in intracellular fluid than in the blood (15, 16). The excretion of thallium is slow; only 3.2% of the body burden is excreted in the urine per day. Approximately the same amount is excreted through the gastrointestinal tract (15).

Symptoms of subacute thallium intoxication are usually slow to appear and early diagnosis is difficult. Of the classic triad of symptoms--gastrointestinal irritation, peripheral neuropathy, and alopecia--only alopecia is characteristic. In acute fatal cases, GI distress is follow by convulsions, motor paralysis, dyspnea, and death in about thirty hours (1, 2, 6-9, 13-16).

The minimum lethal dose in human adults has been estimated at 9-14 mg Tl/kg. (All doses in this section are based on elemental thallium.) Children appear to be

more susceptible with reports of fatal cases after doses of 6-8 mg Tl/kg (1, 2, 11). Gettler and Weiss (2) report that the minimum lethal dose in dogs is 12 mg Tl/kg.

Several groups have investigated the toxicity of Tl^+ in the rat. The LD_{50} for thallous sulfate given S.C. or I.V. was found to be 15 mg/kg (5) and 10 mg/kg (15) respectively. Two other reports (3, 10) give the LD_{50} of parenterally administered $TlNO_3$ as equal to 16 µg Tl/mg. This value for the LD_{50} is extremely low and is difficult to reconcile with all other reports of acute toxicity of Tl^+ in rats and other species.

4. Toxicity Testing by NEN

A study of the acute toxicity of thallous chloride in mice was conducted at NEN. Following I.V. dose of 20.7 mg TlCl/kg (equivalent to 17.6 mg Tl/kg) the animals showed signs of transient (approximately 15 seconds) apnea and decreased motor activity. However, all mice recovered and there were no deaths.

At lower doses (3.5 mg Tl/kg) no signs of toxicity were observed.

This study confirms that milligram quantities of thallium per kg of body weight are required in order to produce fatal poisoning in rodents.

5. Conclusions

Literature reports of the acute toxicity of thallium in man and animals, as well as tests conducted at NEN in mice, indicate that the diagnostic dose of Tl 201 (1.3×10^{-7} m

has a multi-million margin of safety from the
reported minimum lethal dose in man (6–14 mg/k

Toxicity

6. Munch, J.C. Human Thallotoxicosis. JAMA 102:1929-34 (1934).

7. Gettler, A.O., and Weiss, L. Thallium Poisoning III Clinical Toxicology of Thallium. Amer. J. Clin. Pathol. 13:422-9 (1943).

8. Thyresson, N. Experimental Investigation on Thallium Poisoning in the Rat. Acta Derm Venerol 31:3-27 (1951).

9. Truhaut, R. The Toxicology of Thallium. J. Occup. Med. 2:334-6 (1960).

10. Lund, A. The Effect of Various Substances on the Excretion and the Toxicity of Thallium in the Rat. Acta Pharmacol et Toxicol 12:260-8 (1956).

11. Thienes, C.H., and Haley, T.J. Clinical Toxicology, Lea and Febiger. Philadelphia 1964 pp. 295-6.

12. Skelley, J.F., and Gabrial, K.L. Thallium Intoxication in the Dog. Ann N.Y. Acad. Sci. 1 612-17 (1964).

13. Farley, M. Thallium Toxicity in the Dog. Iowa State Univ. Vet. 27:117-8 (1965).

14. Zook, B.C., and Gilmore, C.E. Thallium Poisoning in Dogs. JAVMA 151:206-17 (1967).

15. Rauws, A.G., Ten Han, M., and Kamerbeek, H.H. Influence of the Antidote Dithiocarb on Distribution and Toxicity of Thallium in the Rat. Arch. Int. Pharmacodyn. 182:425-6 (1969).

16. Browning, E. Toxicity of Industrial Metals, Appleton-Century-Crofts, N.Y. 1969 pp. 317-22.

17. Hart, M.M., and Adamson, R.H. Antitumor Activity and Toxicity of Salts of Inorganic Group IIIa Metals: Aluminum, Gallium, Indium, and Thallium. Proc. Nat. Acad. Sci. USA 68: 1623-6 (1971).

18. Oehme, F.W. Mechanisms of Heavy Metal Toxicities. Clin. Toxicol. 5:151-67 (1972).

19. Thallium, The Lancet. Sept. 7, 1974, pp. 564-5.

Pharmacology

15. Berglay, R.K., Peacock, W.C. and Karnofsky, D.A. Distribution and Excretion of Radioactive Thallium in the Chick Embryo, Rat, and Man. J. Pharm. A/P Ther. 107:178-87 (1953).

16. Lund, A. Distribution of Thallium in the Organism and its Elimination. Acta Pharmacol et Toxicol 12:251-9 (1956).

17. Durbin, P.W., Scott, K.G., and Hamilton, J.G. The Distribution of Radioisotopes of Some Heavy Metals in the Rat. U. of Calif. Public in Pharmacol 3:1-34 (1957).

18. Mullins, L.J., and Moore, R.D. The Movement of Thallium Ions in Muscle. J. Gen. Physiol. 43:759-75 (1960).

19. Galeotti, P.J., and Hammond, P.B. The Uptake of Thallium by Rabbit Erythrocytes. J. Pharmacol. Exp. Ther. 144:215-21 (1964).

20. Witschi, H. Desorption of Some Toxic Heavy Metals from Human Erythrocytes in Vitro. Acta Haemat 34:101-115 (1965).

21. Gehring, P.J., and Hammond, P.B. The Interrelationship Between Thallium and Potassium in Animals. J. Pharm. Exp. Ther. 155:187-201 (1967).

22. Rusznyak, I., György, L., Ormai, S., et al. On Some Potassium-Like Qualities of the Thallium Ion. Experientia 24:809-10 (1968).

23. Kawana, M., Drizek, H., Porter, J., et al. Use of ^{199}Tl as a Potassium Analog in Scanning. J. Nucl. Med. 11:333 (1970).

24. Kayne, F.J. Thallium (I) Activation of Pyruvate Kinase. Arch. Biochem. Biophys. 143:232-9 (1971).

25. Potts, A.M., and Au, P.C. Thallous Ion and the Eye. Invest. Ophthalm. 10:925-31 (1971).

26. Kinsey, V.E., McLean, I.W., and Parker, J. Studies on the Crystalline Lens XVIII. Kinetics of Thallium (Tl^+) Transport in Relation to that of the Alkali Metal Cations. Invest. Ophthalm. 10:932-42 (1971).

27. Raynaud, C., Comar, D., Buisson, M., et al. Radioactive Thallium: A New Agent for Scans of the Renal Medulla. in [Blaufox, M.D., and Funck-Bretano, J.L., (ed.)] Radionuclides in Nephrology, Gruna and Stratton, N.Y., 1972, pp. 289-94.

28. Belgrave, E., and Lebowitz, E. Development of ^{201}Tl for Medical Use. J. Nucl. Med. 13: 781 (1972).

29. Den Hertog, A. Some Further Observations on the Electrogenic Sodium Pump in Non-Myelinated Nerve Fibers. J. Physiol. 231:493-509 (1973).

30. Lebowitz, E., Greene, M.W., Bradley-Moore, P., et al. ^{201}Tl for Medical Use. J. Nucl. Med. 14:421-2 (1973).

Related Procedures

31. Charkes, N.D., Skaroff, D.M., Gershon-Cohen, J., et al. Tumor Scanning with Radioactive ^{131}Cesium. J. Nucl. Med. 6:300-306 (1965).

32. Gunton, R.W., Evans, J.R., Baker, R.G., et al. Demonstration of Myocardial Infarction by Photoscans of the Heart in Man. Am. J. Cardiol. 16:482-7 (1965).

33. Love, W.D., Ishihara, Y., Lyon, L.D., et al. Differences in the Relationships Between Coronary Blood Flow and Myocardial Clearance of Isotopes of Potassium, Rubidium, and Cesium. Am. Heart J. 76:353-5 (1968).

34. Hurley, P.J., Cooper, M., Reba, R.C., et al. ^{43}KCl: A New Radiopharmaceutical for Imaging the Heart. J. Nucl. Med. 12:516-519 (1971).

35. Poe, N.D. Comparative Myocardial Uptake and Clearance Characteristics of Potassium and Cesium. J. Nucl. Med. 13:557-60 (1972).

36. Civandra, R., Braunstein, P., Strauli, E., et al. ^{134m}Cs, A New Myocardial Imaging Agent. J. Nucl. Med. 14:243-5 (1973).

37. Rembilt, D.W., Adolph, R.J., Sodd, V.J., et al. Cesium-129 Myocardial Scintigraphy to Detect Myocardial Infarction. Circ. 48:1242-51 (1973).

38. Strauss, H.W., Zaret, B.L., Martin, N.D., et al. Noninvasive Evaluation of Regional Myocardial Perfusion with Potassium-43. Radiology 108:85-90 (1973).

39. Zaret, B.L., Stanson, R.E., Martin, N.D., et al. Potassium-43 Myocardial Perfusion Scanning for the Noninvasive Evaluation of Patients with False-Positive Exercise Tests. Circ. 38:1234-41 (1973).

40. Botti, R.E., MacIntyre, W.J., and Pritchard, W.H. Identification of Ischemic Areas of Left Ventricle by Visualization of ^{43}K Myocardial Deposition. Circulation 47:486-92 (1973).

41. Poe, N.D. Comparative Myocardial Distribution Patterns After Intracoronary Injection of Cesium and Labeled Particles. Radiology 106:341-46 (1973).

42. ^{43}K Scans at Exercise Show Coronary Perfusion. JAMA 225:461-3 (1973).

43. Strauss, H.W., and Pitt, B. Nuclear Cardiology in Weissler, A.M. (ed): Noninvasive Cardiol Grune & Stratton, N.Y., 1974, pp. 369-400.

Personal Communication

44. Lebowitz, E., Greene, M.W., Bradley-Moore, P., et al. Thallium-201 for Medical Use-I.

45. Bradley-Moore, P., Lebowitz, E., Greene, M., et al. Thallium-201 for Medical Use II Biolog Behavior.

REFERENCES

1. Pachinger, O.M., Williams, A.T., and Bing, R.J. Coronary Blood flow assessment with Xenon and Rubidium. Seminars in Nuclear Medicine, Vol 3, No. 2, Apr 73.

2. Donato, L., Bartolomei, G., and Giordani, R. Evaluation of myocardial perfusion in man with radioisotope potassium and precordial counting. Circulation 29:195, Feb 64.

3. Love, W.D., Romney, R.B., and Burch, G.E. A comparison of distribution of potassium and exchangeable rubidium in the organs of dog using Rb-86. Circulation Research 2:112, 1954)

4. Poe, N. Comparative myocardial uptake and clearance characteristics of potassium and cesium. J. Nucl. Med. Vol 13, No. 7, page 557, Jul 72.

5. Gorton, R.J. Clinical testing of ^{43}K scans of the heart. J. Nucl. Med. 13:432-433, 1972.

6. Zaret, B.L., Strauss, H.W., Martin, N.D. Noninvasive evaluation of regional myocardial perfusion with K-43. New Eng J of Nucl Med. 288:809, Apr 73.

7. Love, W.D., Ishihara, Y., Lyon, L.D. Difference in the relationships between coronary blood flow and myocardial clearance of isotopes of potassium, rubidium and cesium. Am Heart J., 16:353-355, Sep 68.

8. Parker, J.O., Chibny, M.A., West, R.O. The effects of ischemia and alterations of heart rate on myocardial potassium balance in man. Circulation 42:205-217, Aug 70.

9. Bradley, S. The hepatic circulation (1) Handbook of Physiology, Washington, D.C., American Physiological Society, Sec. II, Vol II, 1963, page 1414-1426.

10. Strauss, W.H., Zaret, B.L., Martin, N.D. Noninvasive evaluation of regional myocardial perfusion with K-43 technique in patients with exercise induced transient myocardial ischemia. Radiology 108:85-90, 1973.