

16 Aug 1973

FROM: SGHRI

SUBJECT: Research Proposal

TO: SGS

I. Title: Technetium diphosphonate as a bone scanning agent.

II. Purpose and Background: Technetium phosphate compounds have been established as sensitive and safe scanning agents for the detection of metastatic bone disease.¹⁻⁵ Both technetium-99m polyphosphate¹⁻³ and technetium diphosphonate^{4,5} are currently used in many laboratories of clinical nuclear medicine since these agents: (a) are more sensitive than the classical pharmaceutical, Sr⁸⁵, (b) give a lower radiation dose and, (c) have intrinsically higher resolution.

This laboratory is presently licensed to employ technetium-99m polyphosphate in the detection and delineation of a wide variety of neoplastic and metabolic disorders. It has become apparent that a chemical manipulation of this compound provides additional diagnostic advantages to our armamentarium.^{4,5} This new compound is technetium-labeled stannous-ethane-1-hydroxyl-1, 1-diphosphonate. This agent has been tested in humans and found to be safe and accurate.^{4,5}

We propose to test this radiopharmaceutical in our own radiopharmacy laboratory in an in-vivo animal circumstance with the expectation of employing it in humans, if its performance in animals is established.

The bone-scanning agent presently in use is obtained from Diagnostic Isotopes Inc. (Upper Saddle River, New Jersey). Tagging efficiency as determined by our laboratory is consistently in the range of 50 percent, thus making for a low target to background ratio. We hope to improve on this tag.

The material presently in use costs about \$5.00 per patient. The material we propose to use would cost less than \$1.00, and these savings would be substantial in this high volume screening test if applied to humans.

Our purposes are to manufacture locally a radiopharmaceutical with better quality control and substantially lower cost than the agent presently available to us.

III. Bibliography:

1. Subramanian, G. and McAfee, J.G.: A new complex of ^{99m}Tc for skeletal imaging. Radiology 99:192, 1971.

2. Bell, E.G., Blair, R.J., Subramanian, G. et al: Evaluation of ^{99m}Tc-polyphosphate as a pediatric bone scanning agent (abs). J. Nucl. Med. 13:412, 1972.

3. Murray, I.P.C., McKay, W.J., Robson, J., et al: Skelter, a thermostable ^{99m}Tc agent for skeletal scintigraphy (abs). J. Nucl. Med. 13:455, 1972.

4. Silberstein, E.B., Saenger, E.L., Tofe, A.J., et al: Imaging of bone metastases with ^{99m}Tc -Sn-EHDP (diphosphonate) ^{18}F , and skeletal radiography. Radiology 107:551-555, 1973.

5. Pendergrass, H.P., Potsaid, M.S., and Castronovo, F.P., Jr.: The clinical use of ^{99m}Tc -diphosphonate (HEDSPA). Radiology 107:557-562, 1973.

6. Toxic Substances List, U.S. Dept of Health, Education and Welfare, 1972 edition, Rockville, Maryland, p 513.

7. Weiss, T.W., Fisher, L. and Phang, J.M.: Diphosphonate therapy in a patient with myositis ossificans progressiva. Ann Int Med. 74:933, 1971.

IV. Technical Approach: Diphosphonate (SEHD) will be procured from Monsanto Chemical Corp. and technetium eluted from a Mallinckrodt molybdenum-technetium generator. The diphosphonate will be labeled with technetium in an acid-stannous chloride environment. The extent of tag will be determined by chromatography. Tests for pyrogenicity will be performed by the Limulus technique. Sterility will be ensured by passing the material through a 0.22 micron millipore filter.

The specific activity of the final product will be a matter of experimentation, but we will aim toward the activity of a commercial product, MPI Bone Scintigraphin Reagent (Medi-Physics, Emeryville, California) which contains 0.5 mg of phosphate with a technetium content of 5-15 mCi.

We will perform whole body bone scans on each of approximately 20 adult rabbits. Scanning will be performed at varying intervals up to 4 hours. Comparative scans using our present agent Tc-polyphosphate will be made on approximately half the rabbits. We will make blind scan interpretations of the two pharmaceuticals Tc-diphosphonate and Tc-polyphosphate.

Adverse effects from Tc Sn-EHDP have not been reported. The amount of tin contained in the final preparation (0.2 mg $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}/\text{ml}$) is well below the toxic level.⁶ The amounts of EHDP used (1 mg/ml) are below those employed therapeutically.⁷ The rabbits will be observed after scanning and any apparent adverse effects will be noted. Necropsy will be performed on any animal that succumbs in the immediate time surrounding the study.

Whole body scans are performed with the Anger camera by integration of individual area views.

V. Equipment and Supplies: All equipment is on hand. The diphosphonate has been supplied at no cost by the Monsanto Chemical Corp. The technetium will be that eluted from our clinical generator at \$.13 per millicurie.

TcO ₄ @ \$0.13/mCi	\$13.00
Adult rabbits @ \$7.00	<u>140.00</u>
Total	\$153.00

VI. Investigative Schedule: Estimated time to completion will be 6 months.

VII. Experimental Subjects: All animals will be handled in accordance with AFR 169-2.

VIII. N/A

IX. Personnel Data:

Medical Center Commander	Paul W. Myers, Brigadier General, USAF, MC
Principal Investigator	William C. Harvey, Lt Colonel, USAF, MC
Associate Investigator	Mary Lou Brown, Capt, USAF, (BSC)

X. Manpower:

Lt Col	AFSC 9836	5 hours duty time, 10 hours off duty time
Capt	AFSC 9246	20 hours duty time, 20 hours off duty time

WILLIAM C. HARVEY, Lt Col, USAF, MC
Chief, Nuclear Medicine Department