

U.S. DEPARTMENT OF ENERGY
FIELD TASK PROPOSAL/AGREEMENT

1. WORK PACKAGE NUMBER	2. TASK NO.	3. REV. NO. 0	4. PROJECT NO.	5. DATE PREPARED 04/16/84	6. CONTRACTOR NUMBER MO-9 (000033)
7. TASK TITLE Development of Techniques and Methods for Medical Application and...			8. WORK PACKAGE TITLE		
9. BUDGET AND REPORTING CODE HA-02-07-01	10. TASK TERM Begin: Continuing End: Open		11. CONTRACTOR NAME ASSOCIATED UNIVERSITIES, INC. BROOKHAVEN NATIONAL LABORATORY		12. CODE <i>(see instructions)</i> BNL
13. CONTRACTOR TASK MANAGER <i>(Name: Last, First, MI) (FTS No.)</i> Cohn, Stanton H. (FTS 666-3591)			14. PRINCIPAL INVESTIGATORS <i>(Name: Last, First, MI)</i> Cohn, Stanton H. (FTS 666-3591)		
15. WORK LOCATION <i>(See instructions): Name of facility, City, State, Zip Code</i>			16. Is this task included in the Institutional Plan? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	17. Does this task include any management services efforts? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	

18. TASK DESCRIPTION *(Approach, relation to work package, in 200 words or less)*

The objective of this program is to improve current nuclear techniques and to develop new ones for the analysis and solution of medical problems, and those associated with environmental pollution. Measurement facilities developed, to date, include a unique whole body counter (WBC); a total body neutron activation facility (TBNA); a partial body (prompt gamma) neutron activation facility (PGNA); nuclear resonance scattering techniques for in vivo measurement of metals; an absorptiometric technique for measuring bone density and an in vivo x-ray fluorescence technique for bone Pb. These new techniques provide data in numerous clinical studies not previously amenable to investigation. The development and perfection of these techniques provide unique applications of radiation and radioisotopes to the early diagnosis and evaluation of therapy in human disease.

The PGNA technique has been developed and calibrated for the in vivo measurement of cadmium and mercury. Prompt gamma neutron activation, x-ray fluorescence, and nuclear resonance scattering techniques are being investigated for in vivo measurement of other toxic metals: silicon, beryllium, and lead. Cardinal to all toxicological studies of Cd and other metal pollutants is an accurate and sensitive noninvasive technique for measuring organ burdens. A variation of the prompt gamma neutron activation technique for measuring total body nitrogen has been developed to study interrelationships among cancer, nutrition, and body composition.

In keeping with the mission of Brookhaven, these facilities have been made available to qualified scientists and members of the medical community throughout the world, as indicated by the published reports of collaborative research projects.

19. CONTRACTOR TASK MANAGER

Stanton H. Cohn
Stanton H. Cohn *(Signature)*

04/16/84

(Date)

20. DETAIL ATTACHMENTS. *(See instructions)*

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|--------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> a. Facility Requirements | <input checked="" type="checkbox"/> d. Background | <input checked="" type="checkbox"/> g. Future accomplishments | <input type="checkbox"/> j. Explanation of milestones |
| <input checked="" type="checkbox"/> b. Publications | <input checked="" type="checkbox"/> e. Approach | <input checked="" type="checkbox"/> h. Relationships to other projects | <input type="checkbox"/> k. ZBB Detail |
| <input checked="" type="checkbox"/> c. Purpose | <input checked="" type="checkbox"/> f. Technical progress | <input checked="" type="checkbox"/> i. Environmental assessment | <input checked="" type="checkbox"/> l. Other (Specify):
Capital Equipment |

HA-02-733

1065904

DOE/EO

TITLE Development of Techniques and Methods for Medical Application and Environmental Health Problems	BUDGET AND REPORTING CODE HA-02-07-01		DATE PREPARED 04/16/84	
ASSOCIATED UNIVERSITIES, INC. BROOKHAVEN NATIONAL LABORATORY	CODE BNL	WP NUMBER	TASK NO.	REV. NO. 0

20. Detail Attachments.

a. Facility Requirements.

It is anticipated that work for this proposal will use existing Laboratory facilities and site utility services.

b. Publications.

Cohn, S. H. In vivo neutron activation analysis: Principles and clinical applications. Proc. 3rd World Congress of Nuclear Medicine and Biology, Nucl. Med. and Biol. Advances, C. Raynaud, Editor, Vol. 1, pp. 1049-53, Pergamon Press, Oxford, New York, 1983.

Yasumura, S., Cohn, S. H., and Ellis, K. J. Measurement of extracellular space measured by total body neutron activation. Am. J. Physiol. 244, R36-R40 (1983).

Vaswani, A. N., Vartsky, D., Ellis, K. J., Yasumura, S., and Cohn, S. H. Effects of caloric restriction on body composition and total body nitrogen as measured by neutron activation. Metabolism 32, No. 2, 185-8 (1983).

Tothill, P., Smith, M. A., and Cohn, S. H. Whole-body and part-body turnover of ^{85}Sr in Paget's disease. Phys. Med. and Biol. 28, 149 (1983).

Cohn, S. H., Vartsky, D., Yasumura, S., Vaswani, A. N., and Ellis, K. J. Indexes of body cell mass: Nitrogen versus potassium. Am. J. Physiology 244, E305-10 (1983).

Vartsky, D., Wielopolski, L., Ellis, K. J., and Cohn, S. H. High count rate problems in elemental analysis using pulsed neutron inelastic scattering. Nucl. Instruments and Methods 206, 575-80 (1983).

Aloia, J. F., Vaswani, A., Yeh, J. K., Ellis, K. J., and Cohn, S. H. Sodium excess in post-menopausal osteoporosis. Metabolism 32, 359-62 (1983).

Wielopolski, L., Rosen, J. F., Slatkin, D. N., Vartsky, D., Ellis, K. J., and Cohn, S. H. Feasibility of non-invasive L x-ray fluorescence analysis of lead in the human tibia by soft x-ray fluorescence. Med. Phys. 10, 248-51 (1983).

Cohn, S. H., Aloia, J. F., Vaswani, A. N., Zanzi, I., Vartsky, D., and Ellis, K. J. Age and sex-related changes in bone measured by neutron activation. Osteoporosis: Proc. Int. Symp. on Osteoporosis; Jerusalem, 1981, J. Menczel, G. C. Robin, M. Makin and R. Steinberg, Editors, pp. 33-43, John Wiley, New York, 1983.

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1065905

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TITLE Development of Techniques and Methods for Medical Application and Environmental Health Problems	BUDGET AND REPORTING CODE HA-02-07-01		DATE PREPARED 04/16/84	
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20. Detail Attachments cont.

b. Publications cont.

Cohn, S. H. Clinical applications of in vivo neutron activation analysis. 15th Annual Intra-Science Res. Symp. on "Non-Invasive Studies of Body Chemistry," W. Wolf, Editor, Raven Press, New York 1983 (in press).

Ettinger, K. V. and Cohn, S. H. Future studies of elemental composition by in vivo neutron activation analysis. 15th Annual Intra-Science Res. Symp. on "Non-Invasive Studies of Body Chemistry," W. Wolf, Editor, Raven Press, New York, 1983 (in press).

Lessard, E. T., Miltenberger, R. P., and Cohn, S. H. Internal exposure from ^{137}CS , ^{65}Zn , ^{90}Sr , ^{55}Fe and ^{239}Pu in Marshall Island residents, Proc. Int. Dosimetry Symposium, Health Physics Society, Harrisburg, 1982 (in press).

Lessard, E. T., Miltenberger, R. P., Musolino, S. V., Conard, R. A., and Cohn, S. H. Protracted exposure to fallout: The Rongelap and Utirik Experience. New Eng. J. Med., submitted.

Applications of nuclear techniques for the in vivo body composition studies at Brookhaven National Laboratory. IAEA Panel Report on Nuclear Based Techniques for in vivo study of Human Body Composition - June, 1981 (in press).

In vivo neutron activation analysis, Chap. 17 Textbook of Nuclear Medicine, 2nd Edition, A. F. G. Rocha and J. C. Harbert, Editors, Lea and Febiger, Philadelphia, (in press).

Ellis, K. J., Yuen, K., Yasumura S., and Cohn, S. H. Dose-response analysis of cadmium in man: Body burden vs. kidney dysfunction. Envir. Res. Feb., in press.

Research Opportunities in Bone Demineralization., S. A. Anderson and S. H. Cohn, Editors, Life Science Division, Office of Space Science and Applications, NASA, Washington, DC, 1983 (in press).

Aloia, J. F., Vaswani, A. N., Kapoor, A., Yeh, J. K., and Cohn, S. H. Treatment of osteoporosis with calcitonin. Metabolism, submitted.

Vartsky, D., Ellis, K. J., Wielopolski, L., and Cohn, S. H. Decay of ^{75}mAs , Letter to Editor. J. Radiation Isotopes, accepted.

Cohn, S. H., Vaswani, A. N., Yasumura, S., Yuen, K., and Ellis, K. J. Improved models for determination of body fat by in vivo neutron activation. Am. J. Clin. Nutr., in preparation.

Wielopolski, L., Ancona, R., Vartsky, D., Vaswani, A., Mossey, M., and Cohn, S. H. Nuclear resonance scattering measurement of human iron stores. Blood, J. Am. Soc. Hematology, submitted.

HA-02-737

1065906

DOE/10

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20. Detail Attachments cont.

c. Purpose cont.

initial technique developed at BNL employed two encapsulated sources of 45 Ci of ^{238}Pu , Be, Ge(Li) detectors, and a fast counting circuit. The system has been improved by changing to ^{252}Cf and using better shielding such that the dose is approximately 1/3 of the original system.

The feasibility of using this technique and a nuclear scattering technique to make similar measurements of other trace metals (mercury, copper, silicon, lithium, iron) has also been investigated. The "portable" nature of the neutron sources has made possible the building of a transportable prompt gamma neutron activation facility which can be moved to specific populations of interest.

B. Nitrogen

A new noninvasive technique for measuring total body nitrogen was developed specifically to measure the body protein content and its changes in cancer (NIH-NCI Contract Y01-CP-80207). The method utilizes the technique of measuring, on line, the capture of gamma rays arising from the interaction of neutrons and various elements in the body. The neutrons are derived from a 90 Ci ^{238}Pu , Be source. The gamma detectors in this technique are large volume sodium iodide. Total body nitrogen is measured with a very low dose (26 mrem). The technique offers a new experimental approach for the study of metabolic disorders.

II. Nuclear Resonance Scattering (NRS)

The quantification of body stores of iron rests on a newly developed technique of in vivo nuclear resonance scattering (NRS). In this technique the nucleus of ^{56}Fe (92% isotopic abundance) is raised to its first excited state by gamma radiation. The excited nucleus decays to its ground state by emission of a 847 keV gamma ray. This gamma ray is measured externally to the body by special detection instrumentation.

An instrument to measure small amounts of iron was constructed and used in phantom studies to demonstrate the feasibility of the technique for measuring tissue-deposited iron. A full scale instrument capable of measuring low levels of iron in the heart and liver of thalassemic patients was developed. The calibration and testing of this NRS instrument was completed in phase 1 of the study.

In phase 2, the instrument is to be used to measure changes in iron deposits in thalassemic patients currently undergoing chelation therapy in research studies in the Boston and New York areas. Patients will be brought to Brookhaven at 6-12 month intervals for measurement. In addition, patients on hemodialysis with hemosiderosis are being studied.

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20. Detail Attachments cont.

d. Background cont.

1.8 µg/g Cd in the liver and 1.5 mg Cd for one kidney. The facility has been mounted in a 34 ft. trailer which, complete with medical examination facilities, can be moved to any site to study industrially exposed populations.

The measurement of total body nitrogen by prompt gamma neutron activation was first originated by Rundo of Harwell. In recent years, the technique was further developed by the University of Birmingham, England group. At BNL, neutrons from ^{238}Pu , Be or ^{252}Cf "portable" sources are used in place of the cyclotron neutrons used by the Birmingham group.

The feasibility of measuring liver burdens of cadmium in vivo was first presented by Harvey et al. in Lancet, June 7, 1975. They use a pulsed beam of cyclotron neutrons, while the BNL system employs "portable" sources of ^{238}Pu , Be or ^{252}Cf . There are numerous advantages to the use of "portable" sources for the measurement of both nitrogen and cadmium, such as ease of operation and the possibility of locating the facility in a clinical environment. In addition, a higher precision and lower radiation dose to the subject is possible with this technique. Further, the portable nature of the ^{238}Pu , Be and ^{252}Cf sources permits the use of mobile activation facilities that can be brought to the population of interest easily and economically.

e. Approach.

R&D Methodology

The work is conducted as described in sections 20c., 20d., and 20f., and is in conformance with generally accepted methodology for investigations of this character.

Management Controls

Fiscal control will be exercised in the form of monthly comparisons, over the task term, of actual costs incurred against corresponding line items of the budget. Technical results shall be monitored through a periodic review, by the Contractor Task Manager, of accomplishments by measuring actual performance as compared to expected progress. All work shall be conducted in conformance with generally accepted standards for R&D and other investigative or analytic procedures, as observed by universities and large independent research facilities including Brookhaven National Laboratory.

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20. Detail Attachments cont.

f. Technical Progress cont.

Technical Progress in FY 1983 cont.

2. The next phase of this project was to examine the relationship between body burden and estimates of the inhalation conditions at a cadmium smelter. In vivo measurements of kidney and liver cadmium for 82 industrially exposed workers were used to determine body burden. Personal work histories, area monitoring data, and personal air sampling monitor data were combined to provide individual exposure estimates (TWE). The body burden data were compared with the total inhalation exposure estimates. The following relationships were found:

$$KCD = 75.6 \ln TWE - 165.6$$

and

$$LCD = 8.43 \ln TWE - 22.8$$

The frequency of abnormal kidney dysfunction was also examined in terms of the exposure estimates. A logistic dose-response was obtained with the following equation:

$$\text{logit } p = 1.232 \ln TWE - 8.34$$

where p is probability of having kidney dysfunction. When this curve was examined further, it was evident that a significant increase in kidney dysfunction occurs at exposures above 400-500 $\mu\text{g}/\text{m}^3 \times \text{yr}$.

3. An improved instrument was developed for the measurement of liver and kidney cadmium by in vivo neutron activation analysis in both occupationally and environmentally exposed persons. Detailed calibrations of the instrument were made in a study of 50 male workers at an industrial plant in Cleveland this year. The importance of accurate organ localization by ultrasound is stressed, without which errors of 40 and 25% in individual and group kidney measurements, respectively, can occur. The detection limit is 1.5 mg cadmium in the kidney and 1.8 mg/g (wet weight) in the liver for a local dose of 2.0 mSv. This instrument, therefore, combines the advantages of portability with high sensitivity of detection of cadmium. Further, the employment of ^{252}Cf neutron sources avoids the difficulties involved in transporting Pu sources through New York City.

II. Nuclear Resonance Scattering

A technique for the measurement of body iron utilizing nuclear resonant scattering of gamma rays has been developed and validated. From this prototype study, a full scale facility was developed and applied in a clinical study. Photons (847 keV) emitted from a gaseous $^{56}\text{MnCl}_2$ source (prepared in the BNL Medical Reactor) are scattered resonantly from ^{56}Fe present in the liver and heart. The spatial uniformity of activation, the sensitivity of the detection system, and the limits of detection have been investigated. Measurements were made on a liver, heart phantom and 30 thalassemic patients. The resonance scattering technique

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20. Detail Attachments cont.

f. Technical Progress cont.

Technical Progress in FY 1983 cont.

Measurements will be made on six-hundred normal white women, age 20-80 years, of bone mass and of the putative determinants of osteopenia. Half these women will have the bone mass measurements repeated annually for 4 years. The same measurements will be made in 100 women with the crush fracture syndrome and 100 women with fractures of the femur. As a result of this study, it should be possible to make recommendations as to how to maximize skeletal mass and prevent fractures of the proximal femur and spine.

B. The influence of 1,25(OH)₂ vitamin D (ROCALTROL) administration on bone marrow and other parameters of calcium homeostasis in osteoporotic patients is being evaluated. This is part of a multicenter study by Hoffman LaRoche to evaluate the efficacy of this new vitamin. This is a collaborative study between Brookhaven and Nassau Hospital (Dr. J. Aloia). To date, 42 patients have been studied.

C. Evaluation of Body Composition and Nitrogen Distribution in Renal Patients on Chronic Dialysis

Total body protein (nitrogen), lean body mass (potassium), fat and water were measured in renal patients on hemodialysis. Nitrogen was measured by means of prompt gamma neutron activation analysis; total body water was determined with tritium-labeled water, and potassium was measured by whole body counting.

When adjusted for body size, the protein store and lean body mass of the renal patients were within the normal range. Thus, although the mean body weight of the male renal patients was lower than that of normal males, their body proportions were essentially normal. This finding suggests that new standards of nutritional status are needed for patients with renal failure.

It was concluded that it is particularly important to measure protein stores of uremic patients with low dietary intake to ascertain nutritional status. The essential normalcy of the patients studied suggests that dialysis minimizes any residual effects of uremic toxicity or protein calorie malnutrition. Finally, the use of in vivo measurement of total body nitrogen and potassium for determination of body composition provides a simple, direct, and accurate assessment of the nutritional status of uremic patients on dialysis.

D. Other Therapies

The study of the effects of combination therapy (with growth hormone and calcitonin) which simultaneously stimulates bone formation and inhibits bone resorption in osteoporotic patients was continued. To date, 100 patients were studied before and after one-to-two years of growth hormone-calcitonin therapy.

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20. Detail Attachments cont.

f. Technical Progress cont.

Expected Progress in FY 1984 cont.

IV. New Nuclear Techniques

Development of a new technique for the in vivo measurement of total body carbon and possibly oxygen has been initiated. The source of neutrons for this study is a miniature neutron generator currently on loan from Sandia. It is planned to study phantoms first and eventually to construct a patient activation facility. This will require a modification of the pulse rate from 100 pulse/sec to 2000 pulse/sec for the generator. This can be accomplished by Sandia Labs via DOE contract.

Medical application of the gamma radiation generated by the UV ring of the NSLS is being investigated. Photoactivation will be used for the measurement of C, N, and O. The main advantage of this technique is its narrow energy distribution of gamma rays which permit tissue composition measurements in vivo.

Expected Progress in FY 1985.

The general objectives will be as indicated above. The major studies proposed are of several years duration. The trailer-mounted PGNAA facility has been modified to employ ^{252}Cf in place of ^{238}Pu , Be for ease in moving around the country. Several field studies of workers in Cd battery plants and other industrial sites are being planned.

PGNAA, inelastic scattering, and nuclear resonance scattering techniques are being developed for in vivo measurement of toxic metals (mercury). Cardinal to all toxicological studies of Cd, Si, Be, Pb, and other metal pollutants is an accurate and sensitive noninvasive technique for measuring organ burdens.

The PGNAA technique for measuring TBN will continue to be used to study inter-relationships among nutrition and body composition in normal subjects, surgical patients, cancer patients, and obese subjects on various diets.

In keeping with the mission of Brookhaven, these unique facilities will be made available to qualified scientists and members of the medical community throughout the country as in the past.

Expected Progress in FY 1986.

Studies will be designed in order to accomplish the various aims discussed in this task proposal. Specific direction for FY'86 will be determined by the results obtained during FY'85 and by the amount and type of resources available for this task.

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HA-02-749
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20. Detail Attachments cont.

f. Technical Progress cont.

Technical Progress in FY 1983 cont.

C. In Vivo Measurement of Lithium in the Brain

A method for in vivo measurement of lithium levels in the human brain was developed. In this technique, the brain is irradiated with neutrons and ^6Li present in the brain interacts with neutrons by the $^6\text{Li} (n, \alpha) \text{T}$ reaction resulting in energetic recoiling tritium atoms. Since the tritium in the form of HT is quite inert and its solubility in body tissues and fluids is small, the gas is readily exhaled. The tritiated hydrogen exhaled is isolated from other gases in the breath and counted in a low-background proportional counter.

To date, the performance of the system has been investigated by examining the quantitative measurement of the recovery of hydrogen, "tritium" background in unexposed individuals, and the natural background of the counters. A patient treated with therapeutic levels of Li will exhale tritium activity of about 70c/day after receiving a neutron dose of about 1 rem to the brain containing approximately 1 mg of Li. If ^6Li is used as a drug, the activity will increase to 900c/day.

Currently, it is planned to perform animal studies (on sheep) on the exhalation rate of tritium and establish conversion constants and calibration procedures using phantoms.

Expected Progress in FY 1984.

I. Prompt Gamma Neutron Activation Analysis (PGNAA)

A. Cadmium

The study of the relationship between high liver and kidney concentrations of Cd and kidney damage in industrially exposed workers in a plant in Cleveland were concluded with the use of the prompt gamma facility. Approximately 50 workers were examined. These workers were identified by a NIOSH survey of the plant. Exposures were moderate yet significantly higher than environmental or cigarette-smoking-related levels. A complete workup of these workers will be completed in FY84.

A major question concerning health researchers is the critical concentration of cadmium in the liver and kidney. A paucity of data has resulted from the lack of an adequate technique for in vivo measurement of Cd. With the mobile prompt gamma neutron activation facility, further field studies will be performed to obtain data on the levels of Cd in various groups of industrial workers.

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20. Detail Attachments cont.

1. Capital Equipment Requirements for FY 1986 cont.

mode of operation, four NaI (large volume) detectors and their associated electronics (\$25,000). The present generator has a maximum pulse rate of 100 pulse/second; this will need to be increased to 2000 pulse/second (\$87,000).

It is planned that the photon activation program being developed at Brookhaven in collaboration with the National Synchrotron Light Source (NSLS) Department to measure C, N, and O via (γ, N) reactions will require the following devices: NaI detector (\$7,000), computer-controlled pulse-height analyzer (\$28,000), electronics for counting at high count rates (\$15,000).

An x-ray machine (\$25,000) will be needed to improve the sensitivity of the x-ray fluorescence technique which is used for in vivo Pb measurements. The machine will be used to provide a filtered, polarized x-ray beam.

The 54 detectors used in the Whole Body Counter were originally built in 1967 and now have a failure rate of $\sqrt{10}$ crystals per year. The maximum replacement cost per crystal is \$6,000. Repair costs vary between \$1,000 and \$3,000 per crystal. In FY 1986 \$18,000 is requested for the replacement of detectors.

Expansion of the Department VAX computer system is required since the existing UNIBUS cabinet is fully utilized. Before any additional equipment can be added, a second UNIBUS cabinet is necessary. Additionally, greater input/output performance may be achieved by adding another mass bus interface. This will require another CPU expansion cabinet. The total cost of the proposed expansion allocable to this program is \$6,000.

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HA-02-751

DOE/NO