CONTRACT NO.

AT(11-1)1826

RESEARCH PROPOSAL AND PROGRESS REPORT

March 22, 1974

Uranium Miner Lung Cancer Study

Contractor's Project Director:

Geno Saccomanno

Geno Saccomanno, Ph.D., M.D.
Department of Pathology
St. Mary's Hospital
Grand Junction, Colorado

Site of Research Project:

St. Mary's Hospital
Grand Junction, Colorado

Administrator:

Sister Mary Aloys

Sister Mary Aloys
St. Mary's Hospital
Grand Junction, Colorado 81501

NOTICE

This report was prepared as an account of work sponsored by the United States Government. Neither the United States nor the United States Atomic Energy Commission, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness or usefulness of any information, apparatus, product or process disclosed, or represents that its use would not infringe privately owned rights.

MASTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency Thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.

RESEARCH PROPOSAL AND PROGRESS REPORT

March 22, 1974

Contract No. AT(11-1)1826

Uranium Miner Lung Cancer Study

This contract covers five facets of research work. The progress made in the last six and one-half years is substantial, and request is made that the contract be renewed for another year. The description of the objectives is the same as last year. The figures are varied according to our accomplishments to date. A summary of the accomplishments on each project is as follows:

I. Main Research Accomplishments:

A. Tumor Registry

Two hundred twenty cases have been accumulated and include the following items:

1. All of the smears made from sputum on each case are properly recorded and filed. Over 200 sputum slides are part of the registry for some cases.
2. Slides from all tissue sections, including biopsies, and the autopsy material, including the serial sections of lungs which are prepared by Dr. Oscar Auerbach, are filed with each case.
3. Complete hospital charts, exclusive of the nurse's notes, are available with each case.
4. Autopsy reports, including the gross and microscopic, are a part of each case.
5. The tracheobronchial tree has been studied and recorded in 81 of the 220 uranium miners who are in this registry.

The accumulation of this material should be continued, for there is nothing in the world like it. Here is a collection of radiation and cigarette induced tumors for study in many dimensions. I believe that representative samples of tissues from these cases should be sealed in glass for analysis, if further experimental data might be elected for research sometime in the future. The number of uranium miners dying from radiation and cigarette smoking was thought to be on the decline, but recently some indications suggest otherwise. It may be that the Grants' area and the Plateau populations are becoming mixed, and a new prospective may be in the making. Other carcinogens may be inserted, or is this change in effects due to the latent period on the New Mexico population, preventing the expected decrease in incidence of cancer of the lung among the uranium miners on the Colorado Plateau. I assume that eventually this registry will go to the Atomic Energy Commission offices in Washington, D.C., or probably to the Armed Forces Institute of Pathology. There are many research interests in regard to this population exposed to these toxic agents, and the material will be available to anyone interested in its exploration and analysis.

B. The Manual on Pulmonary Cytology

This endeavor, it seemed, would be completed by this point in time, but material continues to accumulate with the passage of time. We hope that soon we will begin to develop the manuscript. We presently have 973 photomicrographs of tissues and cells arranged and presented in an acceptable parade of pictures showing normal pulmonary and bronchial histology in infants and adults. This displays all cell patterns found in sputum samples from normal to all abnormal states with pictorial procession of abnormal cells to the development of carcinoma-in-situ and eventual progression to invasive carcinoma. This cytology will be presented to facilitate learning the various stages of tumor development. Inflammatory cells and other cells seen in normal pulmonary function will be shown to facilitate the identification of abnormal cells from inflammatory diseases of the lung, both benign and malignant.

We estimate that improvement in some of the photomicrographs will have to be accumulated. In addition, there will be some retakes to improve quality. The dialogue that will be part of the discussion of the pictures has been started. It is felt that the photography should continue to be accumulated, catalogued and put into proper sequence before final commentary is completed. It is hoped that this can be developed as an excellent manual, primarily for the student who wishes to learn about pulmonary cytology and its relation to the development and diagnosis of cancer and inflammatory disease of the lung. Approximately 15,000 photomicrographs have been taken on the photomicroscope.

We continue to present workshops in different cities and under the sponsorship of many organizations, principally the American Society of Cytology, American Society of Clinical Pathologists, and many private hospitals, universities, and societies. A list of the workshops presented to July 1, 1974, are attached. The material presented will be incorporated in the manual. Also, all of the case material developed in our studies of carcinoma-in-situ of the lung and the products of the bronchoscopy studies will be included.

C. Subsequent Sputum Cell Changes in Uranium Miners with Atypical Sputum Cells, Who Have Retired from Uranium Mining or Who Have Quit Cigarette Smoking or Both

The progression of this study is recorded in Charts I and II (attached). This study is progressing very favorably, and we have had fine cooperation from the uranium miners in the study. We started the study with 385 miners and controls and are presently following 201. Some of the miners we started with have expired. Some of those lost to the study have been recorded. We are also following additional miners,* who were considered good cases for

* Charts III and IV

follow-up, with repeat specimens, but they are not considered a part of the initial regression study. Chart I shows that 19 miners in the study have developed malignant lesions and died.

It is very important that this group be continued in this study, for examination of the data available to date leaves many unanswered questions; however, trends are developing that are beginning to appear very revealing.

A total of 760 sputum specimens were examined in 1969, 889 in 1970, 902 in 1971, 931 in 1972, 1055 in 1973, and 229 from January 1 to March 18, 1974. All of these have been processed, read, evaluated, and recorded.

D. Sensory Development for Localization of Carcinoma-in-Situ of the Lung

A study is being developed to determine if a tumor-finding antibiotic (Bleomycin), which is stored by tumor tissue for longer periods than normal tissue, can be tagged with a radioactive substance. Many radioactive tags are considered. Those under consideration are I 125, cobalt, arsenic, and phosphorus. A probe with high sensitivity is being developed under the direction of Mr. Gerald Huth, University of California of Los Angeles Nuclear Laboratory. It is hoped that such a radioactive sensitive antibiotic and probe can be developed. If this can be accomplished, the agents and probes will be tested here at St. Mary's Hospital on patients noted to have carcinoma-in-situ.

- E. If the above radioactive antibiotic can be developed, it is also hoped that this system may be sufficiently sensitive to the performance of liquid scintillation detection of nuclear debris sequestered into sputum samples. From the experience we have developed, we suspect that all malignant tumors, regardless of the site of the primary, continuously shed cells into the circulatory tree with increased frequency as the primary tumor grows. We have good evidence to indicate that these tumor cells that find their way into the circulatory tree are sequestered into the alveolar spaces and gradually work up the tracheobronchial tree and can be demonstrated infrequently as intact cells, but most frequently as cellular debris. If this material can be identified as being of tumor cell debris, we hope we will be able to identify that, indeed, this material is coming from a distant tumor. This may allow us to make a diagnosis of malignancy very early, even before the tumor causes symptoms at its point of origin.

II. Plans for the Continuation of Present Objectives:

Plans are to continue to conduct all five of these studies. Each is equal in importance to the other. All are worthy projects, and it is hoped all will be funded.

III. Students Trained:

Twenty-three students have been trained in our AMA Approved School of Cytotechnology, and eight students are currently enrolled.

IV. Bibliography: See material presented.

V. Present State of Knowledge in This Area of Research:

Our work, as presented above, to our knowledge is the only study of this type being conducted on human beings. No one has a library on carcinoma of the lung from this unique population of uranium miners who are exposed to radiation and other toxic inhalants. This material, in our opinion, certainly should be continued. There are very few manuals on the cytology of the lung, and the preparation of this manual seems very important and is very much needed to teach pathologists as well as cytotechnologists this discipline. The evaluation of the regression of cell abnormalities, if miners cease mining or cigarette smoking or both, certainly should be continued. All of these studies are basic in scope in finding new knowledge on the biology of cancer of the lung and certainly should be continued.

Our studies, described above, in the assessment of radioactive materials for localization of primary tumors of the lung and distant primaries seem most important.

VI. Present Division of Federal Support for Overall Research Program:

These studies are conducted in conjunction with other studies supported by National Institutes of Health-National Cancer Institute-E-72-3233, which are the continuation of studies on sputum cytology in uranium miners and studies on tumors developed by miners. Both of these endeavors must continue if either is to be fruitful in contributing to this most interesting field.

Umberto Saffiotti, M.D., Director of Experimental Carcinogenesis, from the National Cancer Institute was here at St. Mary's Hospital to review our work on August 16, 1971. We believe he was very favorably impressed with our work, for it is truly a study of the biology of cancer of the lung and should yield data which is closely related to all experimental work being done on experimental animals. In fact, our human studies are correlating with the findings on carcinogenesis of lung tumors on the dogs and hamsters exposed to radiation and cigarette smoke at Battelle Northwest Laboratories and the studies presently being conducted at Oak Ridge National Laboratory on the carcinogenesis of lung cancer on rats, mice, and hamsters.

A manuscript on the development of carcinoma of the lung is in preparation for publication. A copy of the manuscript will be sent to Dr. Walter Weyzen, Medical Research Branch, Atomic Energy Commission prior to submission to the publisher.

In summary, these studies are being integrated and have yielded new data and knowledge in the field of lung cancer that will ultimately relate to better patient care and treatment of this disease in man, which presently is the number-one killer after heart disease.

It is hoped that the Atomic Energy Commission will continue to support this project that has made wonderful progress in the past six and one-half years of support.

March 22, 1974

CHART I

REGRESSION STUDY

The Uranium Miner List for the Regression Study (miners with Class II, Stage III or higher sputum) was received from Dr. Victor Archer on January 14, 1969. The 415 miners on the original list were all reviewed and some were reclassified.

1. Original population for study (Doctor Archer's list)	415
a. Total number of miners reviewed that met the criteria of study	246
b. Total number of miners discarded because they didn't meet the criteria of the study	169
c. Total number of miners fulfilling the criteria of the original population and added to the above 246 miners (a) during 1969	139
d. This group was then considered to be the regression study group as of Dec. 31, 1969	385
e. Total number of miners being currently followed	201
f. Total number of miners now inactive (no response, no address, inadequate information, etc., but worked up as much as possible and filed)	134
g. Total number of miners expired since the beginning of the study	50

<u>Year of Death</u>		<u>Cause of Death</u>	
Expired prior to study	1	Carcinoma of lung (total)	19
1969	2	Squamous cell	10
1970	6	Adenocarcinoma	2
1971	5	Oat cell	7
1972	8	Carcinoma (other than lung)	2
1973	18	Accident	4
1974	2	Suicide	2
Date unknown	8	Coronary	5
Total	50	Pneumonia	1
		Pulmonary emboli	1
		Pulmonary insufficiency	1
		Pulmonary infarct	1
		Unknown	14
		Total	50

March 22, 1974

CHART II

Irritant Status	Total No. of Cases	No. of Cases Showing Possible Improvement	CIS and Invasive Tumors
UGU Mining, Non-smoker	13	5	0
UGU Mining and Smoking (Control)	46	30	1
Quit UGU Mining and Quit Smoking	18	3	2
Quit UGU Mining Still Smoking	52	14	4
Quit Smoking Still UGU Mining	31	15	2
Non-smoker Quit UGU Mining	11	6	0
Open Pit U Miner Smoker (Control)	4	0	0
Open Pit U Miner Non-smoker	1	1	0
Quit Open Pit U Mining Still Smoking	1	1	0
Open Pit U Miner Quit Smoking	1	0	1
Uranium Mill Workers Smokers 15 Non-smokers 2 Quit Smoking 6	23	8	0
Totals	201	83	10

The above group of uranium miners is the original group selected by Doctors Archer and Saccomanno during the year 1969. All of the above qualified for this study by sputum analysis showing marked atypia or above.

March 22, 1974

CHART III

ADDITIONS 1970 TO PRESENT TIME

(Not Regression Study, but showing marked atypia and being followed on a three-month repeat basis.)

Total number of miners added 1970 to present, active	108
Total number of miners added 1970 to present, inactive (No response, no address, inadequate information, etc., but worked up as much as possible and filed)	23
Total number of miners who have expired from this group	8

<u>Year of Death</u>		<u>Cause of Death</u>	
1969	1	Carcinoma of lung	3
1970	1	Accident	1
1971	1	Coronary	2
1972	1	Unknown	2
1973	3	Total	<u>8</u>
1974	1		
Total	<u>8</u>		

Note: In addition to the six miners with Carcinoma-in-situ (CIS) from Chart IV, another six miners with carcinoma of the lung are currently being followed who had inadequate follow-up prior to diagnosis. One of these men had a lobectomy in 1969 with poor follow-up before and since that time. The others were diagnosed from 1970 to 1973, and two of these are post operative.

March 22, 1974

CHART IV
ADDITIONS 1970 TO PRESENT TIME

Irritant Status	Total No. of Cases	No. of Cases Showing Possible Improvement	CIS and Invasive Tumors
UGU Mining, Non-smoker	16	7	0
UGU Mining and Smoking (Control)	36	13	1
Quit UGU Mining and Quit Smoking	11	2	1
Quit UGU Mining Still Smoking	8	3	0
Quit Smoking Still UGU Mining	11	3	2
Non-smoker Quit UGU Mining	3	0	0
Open Pit U Miner Smoker (Control)	6	0	1
Open Pit U Miner Non-smoker	2	1	0
Quit Open Pit U Mining Still Smoking	0	0	0
Open Pit U Miner Quit Smoking	1	0	1
Uranium Mill Workers Smokers 9 Non-smokers 1 Quit Smoking 5	15	3	0
Totals	109	32	6

The above group of uranium miners have been selected for followup because of sputum studies showing marked atypia or above. These miners do not qualify for the original Regression Study because they entered the study after 1969.

March 22, 1974

AT(11-1)-1826

WORKSHOPS AND EDUCATIONAL MEETINGS

October 1, 1972 through June 30, 1974

1. National Cancer Institute Meeting, San Antonio, Texas, October 1-5, 1972 *
2. Annual Meeting of the American Society of Cytology, New Orleans, Louisiana; November 1-4, 1972 (Workshop) **
3. Mesa County Medical Society Spring Clinic, Grand Junction, Colorado, April, 1973 *
4. Western Colorado Allied Health, Grand Junction, Colorado, July 27-28, 1973 **
5. Workshop, Center for Disease Control, Atlanta, Georgia, September 6-7, 1973 **
6. Workshop, American Society of Clinical Pathologists, Chicago Illinois, October 19-26, 1973 **
7. Annual Meeting of the American Society of Cytology, Salt Lake City, Utah, November 7-10, 1973 (Workshop) **
8. Pathology-Cytology Committee of the Lung Cancer Detection Group, Johns Hopkins University, November 30, 1973 *
9. Meeting with Doctors Bennett and Tilman to discuss "Instrumentation of Localizing Lung Tumors", Los Angeles, California, December 12-13, 1973 *
10. 1974 Annual Scientific Meeting, New Jersey Chapter, American College of Chest Physicians, February 27, 1974 (Hoffmann-La Roche, Inc., Nutley, New Jersey) *
11. Workshop, American Society of Clinical Pathologists, Los Angeles, California, March 2, 1974 **
12. Workshop, Medical University of South Carolina, Charleston, South Carolina, April 4-6, 1974 **
13. Mesa County Medical Society Spring Clinic, Grand Junction, Colorado, April 26-27-, 1974 *
14. Workshop, St. Francis Hospital, Wichita, Kansas, May 2-4, 1974 **
15. Workshop, Canadian Society of Cytology, Ottawa, Ontario, Canada, June 16-19, 1974 **

* Educational meetings attended by the Project Director, Geno Saccomanno, Ph.D., M.D.

** Workshop on "The Development of Cancer of the Lung" presented by Geno Saccomanno, Ph.D., M.D.

BIBLIOGRAPHY

1. Kuntz, Albert and Saccomanno, Geno: Reflex Inhibition of Intestinal Motility Mediated through Decentralized Prevertebral Ganglia. J. Neurophysiol 7: 163-170, 1944.
2. Kuntz, Albert and Saccomanno, Geno: Sympathetic Innervation of the Detrusor Muscle. The Journal of Urology 51: 535-542, 1944.
3. Saccomanno, Geno; Van Bruggen, John; Minckler, Jeff and Klemme, Roland: Preparation and Storage of Autopsy Nerve Grafts. Science 100: 436, 1944.
4. Saccomanno, Geno: The Components of the Thoracic Cardiac Nerves. Anatomical Record, 1945.
5. Saccomanno, Geno; Utterback, Robert A.; and Klemme, Roland M.: Anatomic Data Regarding the Surgical Treatment of Angina Pectoris. Annals of Surgery 125: 49-56, 1947.
6. Saccomanno, Geno; Kleinschmidt, C.C. and Murphy, Paul: A Case of "Lymphangitic Carcinoma" of the Lung Diagnosed by Sputum Smear Examination. Diseases of the Chest 17: 273, 1950.
7. Saccomanno, Geno and Waldapfel, Richard: A Study of Tissue Implantations on Embryonated-Egg Membranes. A.M.A. Archives of Pathology 52: 529-545, 1951.
8. Waldapfel, Richard and Saccomanno, Geno: Clinico-Pathologic Studies of Obstructions of the Tear Passages. Transactions of the Pacific Coast Oto-Ophthalmological Society, 1953.

BIBLIOGRAPHY (CONTINUED)

9. Saccomanno, Geno; Saunders, Richard P.; Ellis, Harry; Archer, Victor E. and Wood, Blossom G.: Concentration of Carcinoma or Atypical Cells in Sputum. *Acta Cytologica* 7: 305-310, 1963.
10. Saccomanno, Geno; Archer, V.E.; Saunders, R.P.; James, Lynn A. and Beckler, Patricia A.: Lung Cancer of Uranium Miners on the Colorado Plateau. *Health Physics* 10: 1195-1201, 1964.
11. Archer, V.E.; Carrol, B.E.; Brinton, H.P.; and Saccomanno, G.: Epidemiological Studies of Some Nonfatal Effects of Uranium Mining. *Radiological Health and Safety in Mining and Milling of Nuclear Materials* 1: 21-36, 1964.
12. Saccomanno, Geno; Saunders, Richard P.; Archer, Victor E.; Auerbach, Oscar; Kuschner, Marvin; and Beckler, Patricia A.: Cancer of the Lung: the Cytology of Sputum Prior to the Development of Carcinoma. *Acta Cytologica* 9: 413-423, 1965.
13. Archer, V.E.; Black, S.C.; and Saccomanno, Geno: Urine and Tissue Content of ^{210}Pb and ^{210}Po in Uranium Miners. *Diagnosis and Treatment of Deposited Radionuclides*, 1967.
14. Saccomanno, G.: Radiation Exposure of Uranium Miners. Hearings Joint Committee of Atomic Energy, Congress of the U. S., Ninetieth Congress, Part 1: 619-627, 1967.
15. Saccomanno, Geno; Saunders, Richard P., and Scott, Jerry: Lung Cancer of Uranium Miners. *The Bulletin of Pathology*, August, 1967.
16. Black, Stuart C.; Archer, Victor E.; Dixon, Willard C. and Saccomanno, Geno: Correlation of Radiation Exposure and Lead-210 in Uranium Miners. *Health Physics* 14: 81-93, 1968.

BIBLIOGRAPHY (CONTINUED)

17. Richins, C. and Saccomanno, G: Anatomy of the Peripheral Nervous system. Pathology of the Nervous System 1: 1968.
18. Saccomanno, Geno: Uranium Miners' Health. Appendix 5, Hearings on Safety and Health Standards, Bureau of Labor Standards, U.S. Dept. of Labor, Joint Committee of Atomic Energy Congress, U.S. Ninety-first Congress: 301-316, 1969.
19. Blanchard, R. L., Archer, V. E., and Saccomanno, Geno: Blood and skeletal levels of ^{210}Pb - ^{210}Po as a measure of exposure to inhaled radon daughter products. Health Physics 16: 585-596, 1969.
20. Saccomanno, Geno; Saunders, Richard P.; Klein, M.G.; Archer, V.E., and Brennan, Lola: Cytology of the Lung in Reference to Irritant, Individual Sensitivity and Healing. Acta Cytologica, Vol. 14, No. 7, 1970.
21. Saccomanno, Geno; Saunders, Richard P.; Archer, Victor E.; Auerbach, Oscar, and Brennan, Lola: Metaplasia to Neoplasia, Morphology of Experimental Respiratory Carcinogenesis, A.E.C.
22. Saccomanno, Geno; Archer, Victor E.; Auerbach, Oscar; Kushner, Marvin; Saunders, Richard P. and Klein, M.G.: Histologic Types of Lung Cancer among Uranium Miners. Cancer: March, 1971.
23. Minckler, Jeff and Saccomanno, Geno: Exfoliative Cytopathology. Chapter in General Pathology.
24. Brandom, William F.; Saccomanno, Geno; Archer, Victor E.; Archer, Philip G., and Coors, Marilyn E.: Chromosome Aberrations in Uranium Miners Occupationally Exposed to ^{222}Rn . Radiation Research 52:204-215, 1972

BIBLIOGRAPHY (CONTINUED)

25. Saccomanno, Geno; Archer, Victor E.; Auerbach, Oscar, and Saunders, Richard P.: Environmental Carcinogen Susceptibility and Resistance to the Development of Carcinoma of the Lung. Human Pathology 4: 487-495, 1973.
26. Saccomanno, Geno; Archer, Victor E.; Auerbach, Oscar; Saunders, Richard P., and Brennan, Lola M.: Development of Carcinoma of the Lung as Reflected in Exfoliated Cells. Cancer 33: 256-270, 1974.
27. Saccomanno, Geno: Check Sample - Cytopathology, Carcinoma-in-situ. American Society of Clinical Pathologists.