January 4, 1949

Dr. Shields Warren, Director
Division of Biology and Medicine
U. S. Atomic Energy Commission
1901 Constitution Avenue, N. W.
Washington 25, D. C.

Dear Dr. Warren:

Enclosed please find three memoranda which I trust will answer the questions raised in your letter of December 21, 1948, regarding uranium, polonium, and the clinical metabolism ward. A conference is being held in Cleveland today on thorium, and as a result of this, Dr. Hodge will bring the subject up to date and submit a report which will be forwarded to you in a couple of days.

As you will see from Dr. Howland's memorandum, the expenses of the metabolism ward are borne about equally by ourselves and other agencies. To date we have gained some advantage with regard to patient days, but this inequality may disappear in future.

From Dr. Bale's memo you will note that our group has done practically all of the work on polonium toxicity, including the setting of the present tolerance levels. I think the Dayton laboratory would like us to continue with part of this problem, leaving them principally the exposure of large animals.

The situation on uranium is relatively satisfactory with regard to acute chemical toxicity, but there are many problems awaiting solution with regard to long-term accumulations and associated radioactivity.

I hope that this additional information will answer satisfactorily the questions you had in mind.

Sincerely yours,

Henry A. Blair,
Director

HAB:JW
Encl. (3)

CC: Dr. B. S. Wolf

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This document consists of 4 page(s). Copy number 2 of 6 copies, Series A

18968

January 3, 1949

Memorandum to: Dr. Henry A. Blair

From: William F. Bale

Subject: Dr. Shields Warren's Request for Information Concerning Polonium Research

When the production of polonium in large quantities was undertaken during the war years, the Medical Section of the Manhattan District assigned to the Rochester Project the responsibility for any research necessary for the safety of the production personnel at Dayton. No useable information existed concerning the metabolism or toxicity of this element. The reports of Lacassagne and coworkers were rapidly demonstrated to be in a quantitative sense completely unreliable.

Following the development of reliable methods for polonium analysis, work at Rochester was first concentrated on a study of polonium distribution and of excretory rates in rats following intravenous injection. This work was later supplemented by a study of polonium excretion in six human subjects (victims of leukemia) and a large scale study of the comparative toxicity of polonium, radium, and plutonium in rats following single intravenous injections.

From this work it was possible to arrive at a correlation between the body polonium content of human subjects and the rate of urinary excretion. This method has been in continual use at Dayton for monitoring the body polonium content of production plant personnel. From the comparative toxicity studies, plus calculations based upon the body distribution of radioactivity as experimentally determined, estimates of permissible body content were made.

Preliminary work was also carried out on absorption of polonium through the skin, by way of the gastro-intestinal tract, following inhalation into the lungs, etc.

Several instruments constructed at Rochester were provided the Dayton plants for monitoring purposes.

Results of this research are given in several reports of very limited distribution and are summarized in a Survey Volume for the National Nuclear Energy Series (Division VI, Volume III) which is presumably now awaiting publication as a classified volume.

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55268

To: Dr. Henry A. Blair January 3, 1949

At the Dayton plant it was found that exposure to polonium was so great that numerous individuals had, in fact, greater body concentrations of polonium than our research indicated ought to be permitted. Although by improved methods exposure to polonium has decreased considerably, individuals at Dayton still carry polonium concentrations in their bodies close to the maximum allowable on the basis of our research. A careful survey of the Present Status of Polonium Tolerance Estimations may be found in our recent report under that title (UR-44, October 14, 1948).

Recent and Present Research at Rochester - During the past two years research on polonium has continued at Rochester. It has been found in preliminary work that BAL (British Anti-Lewisite) and related substances somewhat increase polonium excretion in experimental animals and also reduce toxicity as measured by lethal effects. Also we have found that kidney lesions are demonstrable in rats following single doses lower than we had previously realized exerted deleterious effects upon this organ. This lesion, demonstrated histologically, may become a limiting factor in permissible dosage calculations since it is considerably more marked than any permanent blood changes at the same dosage level.

It has also been found that the distribution and excretion of polonium after oral administration may be qualitatively and quantitatively quite different than following administration by the intravenous route. In particular, following oral administration polonium shows a pronounced tendency to accumulate in circulating erythrocytes.

Work Planned for the Future - Work that will be carried out at Rochester in the future is dependent upon what the Medical Section of the Atomic Energy Commission decides is the essential work to be done and where it wishes to assign responsibility for the carrying out of this work. In view of the fact that exposure of plant personnel to polonium still remains relatively high, and is difficult to reduce without further great increases in production costs, there may be considerably more work indicated.

Almost all toxicity studies to date have been carried out on rats, and following single intravenous injections. Perhaps such work should be broadened to include other species, particularly the longer lived dog, should include other than intravenous routes of administration, and should include experiments with repeated administration of polonium more closely simulating the chronic exposure of human subjects. Perhaps blood changes, possible production of sterility, and tumor induction should be investigated more completely.

Little is yet really known about the magnitude of polonium absorption through the lungs, or concerning any detrimental changes

To: Dr. Henry A. Blair January 3, 1949

such as tumor induction that may be induced in this organ at the present permitted exposure levels.

Further studies may be comeday indicated on polonium excretion in human subjects following administration at non-toxic levels. The patients with leukemia studied may not be representative of human subjects as a whole.

Additional work perhaps should be carried out on methods of increasing polonium excretion and decreasing toxicity, to the point that the utility of optimal methods are known as applied to cases of accidental human over-exposure.

Biological research so far conducted has been almost entirely on an empirical basis to answer specific health problems with little attention paid to the chemical nature of polonium or to the nature of polonium metabolism. Such basic work on the metabolism of polonium in the body is perhaps indicated to provide a more sure foundation of basic biochemical and physiological knowledge on which to build an ultimate determination of a safe exposure level.

Finally polonium, because of its relative ease of handling and quantitative measurement, because of its wide and, compared with most other alpha emitting elements, relatively uniform distribution in the body, and because of its convenient half-life, may provide the best tool for a general investigation of alpha ray toxicity. Its acute toxicity, for example, is, on a radioactivity basis, some ninety times as great as radium. This is because radium is rapidly transported and stored in calcified areas where its acute toxicity is not high. Polonium, on the other hand, remains largely in soft tissues.

Future Assignment of Research Responsibility - The unit of the Monsanto Chemical Company engaged in polonium production is in the process of moving to greatly enlarged facilities for the production of polonium. A laboratory to be devoted to biological research in connection with the polonium hazard is included in the plant facilities. On the basis of informal discussions between representatives of the medical group at Dayton, headed by Dr. Svirbely, and the group at Rochester, I believe it was generally agreed that large scale toxicity can better be undertaken in Dayton rather than in Rochester, while Rochester is likely to be better equipped for studies on some aspects of pathological physiology, physiology, pathology, therapeutic methods, and metabolism.

Research on polonium at Rochester now represents the only work underway on toxicity due to alpha radiation. It may be desirable to have such investigative work continue in this project to provide

To: Dr. Henry A. Blair January 3, 1949

experienced personnel for consultative work and to aid in our teaching program.

A disadvantage of work on polonium has been and perhaps will continue to be its classified nature, so that work on this subject does not promise to the investigator the rewards associated with the normal publication of research findings.

Distribution of Reports - The limited distribution of reports on biological studies with polonium mentioned earlier means that in most of the operational and research areas of the Atomic Energy Commission no information is available on the results of the investigative work at Rochester. Some of these results are certainly of interest not only to workers with polonium but to persons interested in other alpha emitting elements and in radiation toxicology in general. This suggests that it is perhaps advisable either to expedite the publication of the classified volume of the National Nuclear Energy Series in which the results of this work is contained, or alternatively to issue the contents of this volume as a classified report from the Rochester area. It is a manuscript of some 700 typewritten pages.

Assignment of Responsibility at Rochester - Work on polonium at Rochester was originally centered in the Division of Special Problems. When a concentration of Rochester Research Divisions occurred about two years ago, this Division was consolidated with the Division of Radiology and renamed the Division of Radiology and Biophysics. They have had the general responsibility of research on medical aspects of ionizing radiations and of materials toxic because of radioactivity.

WFB:mt William F. Bale

THE UNIVERSITY OF ROCHESTER

ATOMIC ENERGY PROJECT

18968

January 3, 1949

Memo to: Dr. Henry A. Blair

From: Dr. Joe W. Howland

Subject: DR. SHIELDS WARREN'S REQUEST FOR INFORMATION CONCERNING THE CLINICAL METABOLISM WARD

For clarity the analysis of the Metabolism Ward of the University of Rochester Medical School is outlined as follows:

A. Cost

1. AEC Expenditure

(a) total cost

(b) costs other than salary

2. Contributions of Medical School

B. Analysis of Total Patient Days

C. Tabular Breakdown of Cases studied in 1948

D. Current Results

E. Proposed Research

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A. Cost

1. AEC Expenditure:

(a) The cost of the Metabolism Ward for the year 1948 is slightly in excess of $26,600. Absolute cost cannot be determined until the expenses of the final period are compiled.

(b) A charge of $5.00 per day per patient to cover cost of food, medicines, x-ray and similar services furnished by Strong Memorial Hospital.

A charge of approximately $50.00 monthly to cover cost of special chemistries, electrophoresis studies on blood protein and the like.

An average charge of $50.00 (± $10.00) to cover cost of transportation of each out-of-town patient from his home to Rochester and return.

Travel charges for professional personnel to scientific meetings according to project regulations. Average cost is $80.00 per trip. Total trips during a single year - five.

Apportional expenses for insurance, telephone, etc., distributed throughout project at large. This problem pays approximately 2.0 - 2.5% of total amount for this type of expenditure monthly.

Cost for apparatus and equipment is shared with U. S. Public Health Service Cancer Research Grant which also supplies 2/3 of the technician services. This cost is neglibible and does not exceed $25.00 monthly.

2. Contributions of Medical School:

An analysis of the contributions of the medical school and the Cancer Research Project (Public Health Service Grant) toward the support of the Metabolism Ward shows the following:

1) In facilities. the department of medicine furnishes the four bed ward, and three laboratories. Chemicals, glassware and supplies are largely purchased by the Cancer Research Project.

2) Salaries (partial) of professional personnel paid by the Department of Medicine, $14,500

3) Salaries of the Cancer Research Group (USPHS) $7,200

4) Use of the chest laboratory (approximately half time in 1948) based on annual cost of $15,000 - $7,500.

Total $29,200

B. Analysis of Total Patient Days:

An analysis of the total patient days in the Metabolism Ward indicates that in 1948 a total of 627 are recorded. A breakdown shows 380 of these were spent on problems of AEC interests and 247 on interests of the Department of Medicine and Public Health Service.

C. Tabular Breakdown of Cases Studies in 1948:

Name	Dates	Diagnosis	Laboratory Tests Performed
	1/1 - 1/12	Acute Rheumatic Fever	
	1/7 - 2/2	Beryllium Poisoning*	Respiratory Studies
	1/8 - 2/7	Beryllium Poisoning*	Respiratory Studies
	2/8 - 2/21	Addison's Disease	
	2/9 - 3/29	Normal (Neurocirculatory Asthenia)*	
	Period I. 2/13 - 2/18 " II. 2/18 - 2/23 " III. 2/23 - 2/28 " IV. 2/28 - 3/4 " V. 3/4 - 3/9 " VI. 3/9 - 3/14 " VII. 3/14 - 3/19		Albumin, Nitrogen, Calcium, Phosphorus, Potassium, Sodium, and Chloride balances.
	3/15 - 3/28	Beryllium Poisoning*	
	Period I. 3/18 - 3/24 " II. Not completed.		Nitrogen balance
	4/3 - 5/27	Beryllium Poisoning*	
	Period I. 4/8 - 4/14 " II. 4/14- 4/20 " III. 4/20- 4/26 " IV. 4/26- 5/2 " V. 5/2 - 5/8 " VI. 5/8 - 5/14		Nitrogen balance with and without testosterone

Name	Dates	Diagnosis	Laboratory Tests Performed
	4/18 - 6/4	Beryllium Poisoning*	
	Period I. 4/23 - 4/29		Nitrogen balance - radioactive sodium exchange
	" II. 4/29 - 5/5		
	" III. 5/5 - 5/11		
	" IV. 5/11 - 5/17		
	" V. 5/17 - 5/19		
	" VI. 5/19 - 5/29		
	5/4 - 6/30	Beryllium Poisoning*	
	Period I. 5/11 - 5/17		Nitrogen balance
	" II. 5/17 - 5/23		
	" III. 5/23 - 5/29		
	" IV. 5/29 - 6/5		
	" V. 6/9 - 6/11		
	" VI. 6/25 - 6/30		
	6/1 - 6/26	Anorexia Nervosa	Nitrogen balance
	8/3 - 9/6	Hodgkin's Disease	
	Period I. 8/6 - 8/12		Nitrogen, Calcium, and Phosphorus balances on varying Nitrogen and Calori intakes.
	" II. 8/12- 8/18		
	" III. 8/18- 8/24		
	" IV. 8/24- 8/30		
	" V. 8/30- 9/6		
	8/7 - 9/13	Cirrhosis*	
	Period I. 8/9 - 8/15		Nitrogen, Calcium and Phosphorus with and without testosterone
	" II. 8/15- 8/18		
	" III. 8/18- 8/24		
	" IV. 8/24- 8/30		
	" V. 8/30- 9/5		
	" VI. 9/5 - 9/11		
	9/7 - 10/8 (1st Stay) 10/26-11/24 (2nd Stay)	Beryllium Poisoning*	
	Period I. 9/15 - 9/21		Nitrogen, Calcium, Phosphorus, Chloride and Sodium balances with and without testosterone
	" II. 9/21 - 9/27		
	" III. 9/27 - 10/6		
	" IV. 10/27 - 11/2		
	" V. 11/2 - 11/5		
	" VI. 11/5 - 11/11		
	" VII. 11/17 - 11/23		

Name	Dates	Diagnosis	Laboratory Tests Perform
	9/15 - 10/23	Metastatic Carcinoma*	
	Period I. 9/18 - 9/24 " II. 9/24 - 9/30 " III. 9/30 - 10/6 " IV. 10/6 - 10/12 " V. 10/12 - 10/17		Nitrogen, Calcium, Phosphorus - Radiation
	9/23 - 10/4	Cushing's Syndrome	
	10/6 - 10/10	Carcinoma of Adrenals - died-	
	10/25 - 11/24	Aleukemic Leukemia	
	Period I. 10/27 - 11/2 " II. 11/2 - 11/8 " III. 11/8 - 11/11 " IV. 11/11- 11/17 " V. 11/17- 11/23		Nitrogen, Calcium, Phosphorus balances.
	11/26 - 12/3	Malignant Melanoma	
	Period not completed		
	11/26 - 12/23	Pulmonary Insufficiency*	
	Period I. 11/28 - 12/4 " II. 12/4 - 12/10 " III. 12/10 - 12/16 " IV. 12/16 - 12/22		Nitrogen, Calcium and Phosphorus balances.
	12/3 - Still on Division	Carcinoma Esophagus	
	Period I. 12/4 - 12/10 " II. 12/10- 12/16 " III. 12/16- 12/22 " IV. 12/30		Nitrogen, Calcium, Phosphorus and Chloride balances.
	12/28	Carcinoma Ovary*	
	Period I. Started 12/30		Nitrogen, Calcium, Phosphorus balances with radiation.

D. Current Results:

Results obtained in the careful study of a series of cases of chronic pulmonary granulomatosis of beryllium workers of varying grades of severity can be outlined as follows.

1) A carefully controlled analysis of the respiratory physiology of this disease has been made and reported, (in cooperation with Department of Medicine), Rochester Report. This series of studies is to be extended.

2) Nitrogen balance studies on a series of patients have shown a faulty absorption of nitrogen as well as indications toward an impaired utilization of nitrogen even after testosterone. This suggests that beryllium poisoning is a generalized rather than solely a pulmonary phenomena. There is also an impairment of liver function. Study of one patient with a similar degree of liver involvement did not show similar changes in nitrogen metabolism.

3) It has been suggested that visceral anoxia may be the cause of the faulty metabolism. Studies are in progress on several cases of anoxia due to pulmonary fibrosis to attempt an answer to this question. Early results indicate no similarity between the two types of cases.

4) Low levels of urinary keto steroids have been observed in all patients with clinical disease.

5) Routine complete testing of hematological and clinical laboratory phenomena are in progress.

6) Two trials of Cytochrome C have been unsuccessful as to furnishing any respiratory benefit.

7) In cooperation with the USPHS study as to the metabolic effect of irradiation (x-ray) on cancerous subjects is being carried out.

E. Proposed Research:

1) Continuation of the metabolic effects of chronic beryllium poisoning.

2) Study of the possible metabolic changes of employees recovered from acute beryllium poisoning.

3) Extension of studies of the metabolic effect of irradiation with Cancer Research Group. It would be appreciated if cases (normal) accidentally irradiated could be referred for study. Of particular interest in this group is the urinary steroid excretion.

4) Other studies as outlined in original proposal for the metabolism unit.

Joe W. Howland, M.D.
Chief, Division of Medical Services

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18968

THE UNIVERSITY OF [redacted]
Atomic Energy Project

January 4, 1949

Memo to: Dr. Henry A. Blair

From: Dr. Harold C. Hodge

Subject: DR. SHIELDS WARREN'S REQUEST FOR INFORMATION CONCERNING URANIUM

It is probable that no other element has ever received the intensive toxicological study that has been accorded uranium. The emphasis has been laid on the development of safety standards for the control of health hazards arising from the contamination of factory and laboratory air with uranium compounds. Masks and respirators have been tested in atmospheres of uranium dusts. Methods for the recognition and control of uranium poisoning have been sought. (Prophylaxis, detection, and treatment are best approached through an understanding of the mechanism of uranium poisoning.) Most of the results of this work have been collected into monographs; the first one, "The Pharmacology and Toxicology of Uranium Compounds, Volume I", describes the short-term toxicity studies and probably will appear in April, 1949; the second one, "Volume II", presents the results of the chronic inhalation studies and will be submitted for publication early in 1949. With such a large amount of experimental work already in hand, it is reasonable to ask what further information is desired, and why it is needed.

The principal reason for extending and amplifying the studies of uranium exposures in experimental animals lies in the radioactivity of uranium and especially of enriched uranium. A complicated addendum arises in connection with exposures to the dust from the atomic pile; here the radioactive hazard is almost entirely due to fission products, but the behavior of the particle may be more characteristic of uranium oxide. During the first years of work on uranium toxicology, attention was centered on the prevention of chemical poisoning. The low radioactivity of uranium reduced the danger of radiation damage in short-term exposures (5 years or less) to a point where it was disregarded. Now that the emergency phase of the use of atomic energy has passed and exposures to uranium compounds are anticipated for the working life-times of industrial and laboratory personnel, long-time tolerance studies should be undertaken in which the search for radiation damage has first importance, and the search for chemical toxicity is relegated to a secondary role.

At present three lines of continued research are clearly indicated: 1) the study of animals exposed to insoluble uranium dusts to observe the tendency for uranium to accumulate in the lungs and pulmonary lymph nodes; 2) the study of animals exposed to soluble uranium dusts to observe the deposition of uranium in the bone; and 3) the elucidation of the intimate mechanism of uranium poisoning at the enzyme level. Each of these three topics will be described briefly as follows:

Insoluble Dusts: Lung Retention

As a result of year-long inhalation studies of animals exposed to atmospheres containing UF_4 and UO_2 dusts, respectively, evidence has been accumulated that indicates that prolonged exposures to air concentrations of 500 μg U/m^3 would not give rise to the typical renal changes of uranium poisoning (chemical effect). However, the deposition of uranium in the lungs and especially in the pulmonary lymph nodes was surprisingly high and might in some individuals be expected to exceed the tolerance for alpha radiation of 50 μg U/gm suggested by Bale (for U with the natural isotopic composition). Calculations from the limited amount of data on this point suggest that the half-life of insoluble uranium in the lung or pulmonary lymph nodes is of the order of 60 to 100 days and a maximum exposure level has been recommended at 200 to 250 μg U/m^3 with the proviso of a 4-weeks vacation. Since the studies to date have not used enriched uranium and since the studies have been limited to one year, except for two or three dogs examined after 2 years, the important relationship between uranium dust concentration and lung retention should be investigated. The development of radiation injury would be the major criterion; however, the possibility of existence of a chronic type of uranium poisoning has never been ruled out and should be carefully explored.

Current studies have been designed to furnish essential information that must be in hand before a really long-time study of the insoluble dusts (presumably UO_2 would be used) can be begun: 1) the relation between particle size and toxicity of UO_2, 2) the lung retention of UO_2 as related to dust concentration and particle size, 3) the means by which UO_2 is removed from the lung, for example by cilliary action, by phagocytosis or by solution, 4) the technics of uranium fume production, 5) the comparison of the toxicity of U_3O_8 to that of UO_2, 6) the characterization of industrial UO_2 dusts; these are all problems basic to a long-time study and are, at present, under investigation. These investigations are also fundamental to the general problems of inhalation toxicology and will be important in the future in the testing of any product. Because so much is known about uranium poisoning, it is possible to get at these general principles, and the experience gained provides a basis for saving time and money in the designing of tests.

The chronic inhalation exposure studies envisioned would employ an enriched uranium representative of the worst hazard encountered in industry or in laboratory disseminated at dust concentrations critically related to the concentration predicted to be free from danger, either as a result of radioactivity or of chemical poisoning. The dust particle size would be chosen on the basis of the characteristic of industrial exposures. Larger animals, for example, dogs, or goats (perhaps monkeys), would be tested over periods up to 10 or more years. By a suitable substitution calendar, a program of serial studies can be instituted simultaneously. A carefully selected and limited group of tests would be applied to experimental animals to measure their responses.

Pile Dust:

In the near future an extension of the pilot studies just beginning on the hazard arising from pile dust may be considered as a special and unusual case of the insoluble dust problem. Are the dust particles principally UO_2 and are there toxicological effects identical with those of UO_2? Can the respiratory protective devices which have been found effective against UO_2 be employed against pile dust? Underlying these questions is a more fundamental one: is the radiation tolerance to point distribution such as would arise from a relatively few dust particles in the lung comparable to that from generalized radiation such as might follow the inhalation of radon or exposure to x- or gamma rays? How the body will treat a complicated physical mixture of the fission products distributed in or on the dust particles is a very intriguing question which will be exceedingly difficult to answer.

Soluble Dusts: Bone Deposition

From the year-long studies of animals exposed to atmospheres containing uranyl nitrate, uranyl fluoride and uranium tetrachloride, data have been derived to indicate that prolonged exposures to atmospheres containing of the order of 50 μg U/m^3 probably would never give rise to the kidney changes of characteristic uranium poisoning. From these studies also, it became apparent that the bone content of uranium increased progressively with exposure and that this is the only site of accumulation of uranium in the body. The question of radiation damage from such a deposit cannot be ruled out without prolonged study. Basic problems such as the factors controlling the deposition and mobilization of uranium are already underway.

A chronic inhalation exposure study to such a material as uranium hexafluoride would permit the observation of the rate and magnitude of uranium deposition in bone over long period, evidences of radiation damage and of chemical damage would be sought. An attempt would be made to define the laws governing the long-time accumulation of uranium in the skeleton.

Mechanism of Uranium Poisoning:

The site of acute uranium poisoning has been carefully investigated: the principle changes occur in the proximal convoluted tubule of the kidney. Some evidences of chronic effects both in the kidney and elsewhere, for example in the hematopoietic system, have been discovered. Uranium has been shown not to exert its poisonous action by combination with SH enzymes, but carboxyl or phosphate groups are implicated. Specifically, certain enzymes concerned with glucose metabolism are inhibited. Since the control of uranium poisoning,

the development of treatment of acute accidental high-grade exposure, the treatment for injury arising from chronic exposure (if any), the discovery of new and more delicate means of detecting injury or of following the degree of exposure, all are best approached through the knowledge of the mechanism of uranium poisoning, a minimal amount of research should continuously be directed along these lines.

Harold C. Hodge

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