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THE UNIVERSITY OF ROCHESTER  
Atomic Energy Project

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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:

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Insoluble Dusts: Lung Retention

As a result of year-long inhalation studies of animals exposed to atmospheres containing  $UF_2$  and  $UO_2$  dusts, respectively, evidence has been accumulated that indicates that prolonged exposures to air concentrations of  $500 \mu g U/m^3$  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  $50 \mu g U/gm$  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  $250 \mu g U/m^3$  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 ciliary 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.

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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  $50 \mu g U/m^3$  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.

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