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Subject (Letter Containing Letters which

Explain Reasons for the Development of The Research Work
of the Health Division

By R. S. Stone

To Members of Health Division

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Human Subjects Project

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March 29, 1945

TO - Members of Health Division of Metallurgical Project.

FROM - Dr. Robert S. Stone.

BEST COPY AVAILABLE

I am enclosing herewith copies of some letters which explain the reasons for the development of the research work of the Health Division, and state the accomplishments up to the present time. It occurred to several of us that the distribution of these letters to a sufficient number of individuals, so that they could show them to academic personnel throughout the Health Division, would be valuable as a means of orienting everyone in the over-all problems.

Specific letters are not attached covering the work of Dr. Hamilton and Dr. Tannenbaum, but the work is covered in a general way and may be covered later by additional letters. The occasion of the letters was a general report to Mr. Compton and he has given his permission for the Health Division members to see this report. Use your discretion in showing this material to the academic people under you.

Yours sincerely,



Robert S. Stone, M. D.
Associate Project Director
for Health.

RSS/v

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March 23, 1945

A. H. Compton

R. S. Stone

RESEARCH ACTIVITIES OF HEALTH DIVISION

In 1942 when the Health Division of the Metallurgical Project was first called into existence the problems presented were, what hazards would come from the development and operation of chain reacting piles and could they be controlled. At that time we had a considerable body of knowledge on x-ray and gamma-ray hazards and a very limited amount of knowledge of neutron hazards. A few radio-active materials had been used in tracer amounts but practically nothing had been done with amounts sufficient to cause serious damage. The morale of the whole Project was at stake. We calculated the anticipated hazards from known facts and extrapolated to the probable permissible levels of exposure.

The contractor and the University agreed at that time that we would be given the opportunity to check our calculations by experiments and so establish the tolerable limits of exposures on solid grounds. Our program to date has been based on accomplishing these aims for tuballoy, fission products, product, neutrons, beta rays, pile gamma rays and other chemically toxic and radioactive substances which might come into the processes of the Metallurgical Project. In addition we have attempted to understand the mechanism by which these agents acted so as to be able to treat anyone who might be over-exposed to any of them. It has been stated that the number of people who might be so exposed would be small but may I point out that the leaders of science in this country have been working on DSM projects where such hazards exist and were they to suffer any serious damage from the peculiar hazards the United States would suffer an irreparable loss. In the scientific world the loss would be analogous to that of killing the generals of the Army.

The biological experimentation has lagged behind the rest of the program of the Project by about one year; the reason for this has been that many of our experiments could not be started until the materials for them could be made available by pile operations. Our investigations of product, both clinical and biological could not start until a sufficient amount was available to allow some for biological studies. The results which we have obtained and will obtain if allowed to continue working are of value not

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alone to the Metallurgical Project but also to any project making use of the materials developed on any of the DSM projects. Consequently, the need for the results does not terminate with the termination of the main objective of the Metallurgical Project as a whole. The personnel at Sites W and Y in particular are involved.

We have found out a great many things since our organization which were not known before and are of extremely great value. May I list a few of these:

1. The fact that tuballoy is relatively safe to handle and use in most of its compounds has been established; a contrary opinion was held at the commencement of the Project.
2. The absorption, organ distribution and method of elimination of the principle long-life fission products have been obtained; these have been studied when they enter the body by mouth, by lungs or by wounds. Most of this information was completely unknown.
3. The effects of the various fission products on the body as a whole and on the particular organs in which they locate has been determined in part. We have found out such items as the following:
 - a) the amount of some radio-elements required to produce early death, as strontium, barium-lanthanum, zirconium-columbium and yttrium,
 - b) the effects of a bone deposited emitter in producing injury, such as strontium and barium, c) the effects on the lung of radio-elements deposited there, such as cerium and, d) the effects on the gastro-intestinal tract of insoluble emitters passing through, such as yttrium.

The information obtained from these experiments is of great value in establishing the dangerous amounts and the tolerable amounts of the materials. The data required in case of offensive or defensive radio-active warfare could be calculated very easily from our findings.

4. Information concerning product is rapidly being accumulated; we now know the acute lethal dose for different methods of administration; the short time effects produced on bone and other tissues and the relationship of product to radium as acute injurious agents.
5. We have established the acute and sub-acute effects of total body irradiation with slow neutrons and beta rays. Such experiments were not possible before Clinton was in satisfactory operation.
6. We have shown that lymphomatous tumors can be produced by deposited strontium in the body as well as by x-ray, gamma-rays and neutrons.

Also that lung tumors can be caused by x-rays and gamma rays and this makes the possible production of tumors by alpha rays from product much more likely. Bone tumors are appearing in animals injected with strontium; ovarian tumors have appeared in animals being irradiated. All of these have been produced in a relatively short time by relatively large doses. Just what doses will be required with longer exposures is not yet known.

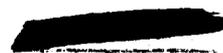
All of these possibilities and others have been suspected by us but now we have shown they are realities and that in case of people with over-exposure we will have to admit the possibility of a connection between the employment and the disease and accept the responsibility.

7. As a means of determining how much product is in the bodies of personnel we have developed fairly satisfactory means of analyzing urine specimens. Methods of analyzing feces, body secretions and tissues are not yet in a satisfactory state.
8. We have developed a satisfactory means of determining the amount of tuballoy in the urine and we have some tests that indicate damage from heavy metals before the trouble has reached clinical levels.
9. Some information has been obtained on the fundamental nature of the injuries caused by radiation and heavy metals, but not enough to know the best methods of treating patients with such injury.
10. We have established the tolerance dose of gamma-rays on a much firmer basis than ever before.

What remains to be done? We have not as yet filled in in sufficient detail the knowledge in any of the fields investigated; in particular we have not established the permissible amounts of radioactive elements which can be allowed to exist in a person's body without danger of complications. We have not satisfactorily determined how to remove many of the damaging materials from the body in case they do become deposited; we have not any satisfactory knowledge of how to treat and restore to usefulness a person who has had an overwhelming effect from radiation.

The establishment of safe levels of air contamination for product and fission products, for safe levels of exposure to fast, slow and thermal neutrons and to beta rays, of safe levels of exposure to other heavy radioactive elements whether transuranic or below uranium remain yet to be established with any degree of certainty.

As an example of the need for the studies which we have under way, I would like to point out two findings which differed markedly from our calculations. First, radiostrontium we knew would be deposited in bone and we thought therefore that bone marrow destruction and bone tumors would be



most likely. We have found that lymphomatous tumors and leukemia were in reality first to appear. This means that we will have to expect leukemias rather than bone tumors as a sub-acute and chronic result of strontium. Second, we expected from calculations based on the energy of product and radium and a somewhat similar metabolic behavior that product would be 1/50 as toxic as radium. We have found that the acute toxicity of product is almost the same gram for gram as radium. Radioautographs have shown us that there is a definite difference in the deposition of product and radium in the bone and this probably explains the greater than anticipated effect. Present indications are that in sub-acute exposures product will not be exactly as toxic as radium and much longer term experiments may show that product is not quite so hazardous as we must assume it to be.

I believe that the biological and clinical research programs of the Metallurgical Project have justified their existence, that the continued use of tuballoy isotopes, fission products and product by DSM projects not only justifies but necessitates the continuation of a large amount of health research work.

Robert S. Stone, M. D.



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March 23, 1945

A. H. Compton

K. S. Cole.

RESULTS OF BIOLOGICAL RESEARCH

Dr. Stone has asked me to submit more specific data to amplify his general report to you on research problems connected with health.

The first objective of the biological research in the Biology Section is to determine the results of exposures of animals to Project radiations and radioactive materials and to estimate the results of exposures of man to these hazards. The more important data and conclusions bearing on this objective are now summarized.

About fifteen percent of the radioactive materials inhaled has been deposited in the lungs. The time required to remove one half of the deposited materials varied from a few seconds to two weeks, for the fission products investigated (I, Sr, Y, Ru, Zr, Ce) and from twelve hours to two weeks for plutonium, while the times for ninety percent removal were about two months for Ce and Pu. These times depend so much upon the element and its chemical and physical form that no generalizations are possible. Fifty microcuries of Ce deposited in rat lungs caused severe lung injuries and killed half of the animals within three months.

It has been found that half of the rats swallowing fifteen microcuries of Y, Sr or mixed fission products per gram of body weight did not live over a month. When about three microcuries of Sr, Ba-La, Zr-Cb, or Y per gram were introduced directly into the bodies of mice, rats, rabbits or dogs half of the animals died in a month. About one-half microgram of Pu or Ra per gram of body weight produced the same result in mice, rats and dogs. For the present it is reasonable to assume that a man will be killed promptly by fifteen microcuries of fission products per gram or a half microgram of plutonium per gram introduced into the body.

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For smaller amounts of material in the body mice live longer, six months for two and a half microcuries of Sr per gram to ten months for half microcurie per gram but they develop an average of fifteen percent bone tumors and twenty-five percent lymphoma and leukemia before death. Similar figures may be available in six months for plutonium.

About 500 r of x-rays has killed half of several strains of mice, rats, rabbits and dogs in a month and we can expect the same effect on man. With fast neutrons the value is about 100 n for mice and rabbits. It has been found that about half of the x-ray injury to rats was gone in a week after an exposure. But 70 r per day also killed rats and mice in a month and 10r per day shortened their lifetime considerably.

Dogs and rabbits which ultimately died in two weeks after x-ray exposure had an immediate prostration followed by gradual loss of red blood cells. After a week the animals lost weight rapidly and developed other symptoms suggesting that death was caused by circulatory failure. Two dogs receiving fatal and near-fatal amounts of plutonium showed the same effects but without the initial prostration.

Blood counts on animals exposed to various radiations and radioactive materials have shown that the lymphocytes were the most sensitive cells in the blood, 100 r of x-rays or 24 n of fast neutrons removed half of these cells while 25 r and 10 n respectively produced minimum detectable effect. About two microcuries of Sr or Ba-La reduced the lymphocytes to half in mice, rats and rabbits while about a half microcurie per gram was detectable. Pu and Ra reduced these cells to half in mice, rats and rabbits at about one-fifth micrograms per gram.

The microscopic examination of tissues from exposed animals showed that fission products and x-ray produced the most damage in the marrow of the bones. The lymphatic tissues, the lining of the gut and the reproductive organs were also damaged. Plutonium caused severe damage to the bone itself while for equivalent exposure, Sr and Ba-La had less effect and x-rays did not produce any detectable damage. The injured tissues recovered more completely from x-ray damage than from that caused by fission products.

In conclusion I wish to summarize the present situation. The major portion of our fact-finding program on the immediate effects of fission products and external radiations is completed. Practically all of our personnel and facilities are now occupied by work on Plutonium and on delayed injuries.

K. S. Cole

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March 24, 1945

A. H. Compton

H. J. Curtis

BIOLOGICAL WORK AT CLINTON LABORATORIES

Dr. Stone suggested I write you regarding some of the results which have been obtained by the biological group at Clinton to supplement his recent letter to you on the aims and accomplishments of the biological program. From the purely biological side, our task here has been to investigate the biological effects of external radiations and other hazards which might exist in the neighborhood of a production pile.

It has been necessary to devise methods for exposing animals to the various radiations in pure form and over a wide range of intensities. The plan of the experiments has been to expose groups of animals to high intensities of a particular radiation and establish the acute lethal dose, and with this knowledge extend the work to lower and lower exposures extending over longer and longer periods of time. Specific findings and the present status of the work with the various radiations are as follows:

Gamma Rays: This radiation has been considered as equivalent to x-rays, about which a good deal is known medically. The other radiations have been compared then with this, both for acute and chronic effects, in order that results could be more easily applied to man. Many experiments are now in progress, essentially acting as controls for experiments with the other radiations.

Fast Neutrons: It has been found that for acute (30 day) death this radiation is 5.0 times as effective as gamma-radiation for equal energy absorption. When administered at a rate of 13 n/day and 4.3 n/day animals

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die after accumulating about three times the acute lethal dose (90 n) but at 1.15 n/day after only 1.7 times the lethal dose. This is faster than for gamma radiation but how much faster is not known since the corresponding gamma ray series are not yet complete. Histological and hematological effects are almost identical with those produced by gamma rays, but the long term series are not complete. For acute effects, gamma rays and fast neutrons are completely additive.

Slow Neutrons: It has been found that 50% of mice will die in about 21 days following an 8 hour exposure to a slow neutron flux of 3×10^8 neutrons/cm²-sec. About one-fourth of this effect is due to capture gamma radiation from hydrogen, and the remainder presumably to proton and C¹⁴ recoil from the reaction $N^{14} (n, p) C^{14}$. These latter are produced preferentially in the nuclei of cells, and so produce maximum damage. Radioactive isotopes formed in the body as a result of exposure are a secondary hazard, of which phosphorus is the most important element, with Na, K and Cl playing minor roles. A few preliminary results on long term effects seem to indicate that this radiation may have very potent carcinogenic action, a hint of which has also been received from histological studies.

Beta Rays: In order to produce death it is necessary to apply about twice as much of this radiation as with gamma rays as measured on an equal energy basis. However, the absorption of gamma rays is proportional to the volume of the animal while with beta rays it is proportional to the surface area. Thus the acute lethal dose of beta rays for mice is 4500 r, for rats 7500 r, and for rabbits 20,000 r at the surface. However, since in this work the real danger from beta rays probably lies in damage to the skin of the hands leading to skin cancer, one, therefore, cannot reason that beta rays are less dangerous than gamma rays. Beta ray ulcers have been produced by local exposure which heal only after several months, and skin cancers have been produced in mice after only a single exposure. Histological studies show a heavy thickening of the skin following recovery, and metabolic studies show that large quantities of body fluids are lost through the damaged skin. Beta rays produce no effect on the blood count.

Other potential hazards in the neighborhood of the Clinton pile have fortunately been found to be negligible. All animals in the buildings and around the grounds are normal in every respect and this work will soon be discontinued. Rabbits have been exposed to the undiluted pile stack gases for about 15 months and are still normal in every respect. From studies on fission recoil isotopes obtained by placing bare uranium foil in the pile, it has been found that the hazard due to the inspiration of these products is a very minor one, and if such products were released in the air the danger would be from external beta and gamma radiation.

It can then be said that perhaps our hardest task, that of developing exposure methods, is complete and that many of our hardest biological

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problems have been solved. Since July 1944 we have been observing the prolonged effects of radiations, and the longer these observations are continued the more information we will have. Results already obtained from these experiments have indicated the desirability of starting a number of new series. I feel that this laboratory is almost uniquely equipped to continue these studies, and that it would be a mistake to curtail them.

H. J. Curtis

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March 25, 1945

R. S. Stone

S. Schwartz

APPENDIX TO LETTER, R. S. S. TO A.H.C. (MUC-RSS-425)

Contributions to Clinical Procedure:

1. A rapid, simple, and extremely sensitive method has been devised for the quantitative estimation of tuballoy. (Sensitive to one hundred billionth of a gram). This method is applicable to biological materials such as urine as well as other sources.
2. Urine T studies of Ames personnel show good correlation with history of T exposure.
3. A significant correlation has been found between the exposure of project personnel to tuballoy, berillium, and other metals and their urinary excretion of coproporphyrin.
4. An increased amount of various urine pigments is excreted by many individuals with chemical, metal, and possibly radiation exposure. By the use of improved techniques we are now attempting to make these tests more specific.
5. A method has been devised for the isolation of white blood cells from venous blood. (These cells are being used for numerous biochemical studies.)
6. A number of project personnel have been shown to have at least borderline abnormalities in their liver function tests. We have not, however, correlated these with certainty with any project exposure.
7. Red blood cells protoporphyrin values have been found to be commonly elevated in individuals with tuballoy as well as with non-tuballoy metal exposure.

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Studies currently in progress (in addition to improvement on the above).

1. Biochemical studies of white blood cells in individuals with radiation exposure.
2. Studies of tissue breakdown products in urine, with special reference to individuals with radiation exposure.
3. Studies of fecal porphyrins in individuals with chemical, metal or radiation exposure.

Sincerely yours,

Samuel Schwartz, M.D.

SS/mjh