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REPORT OF HEALTH ACTIVITIES

under

Contract Number W 7401-eng-37
W 7405-eng-48a
W 7405-eng-48c

MONTH OF JUNE 1945

DECLASSIFIED Per Letter Instructions Of
A 72-2-1-53

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Human Subjects Project

Contract Number W 7401 - eng - 37
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HEALTH DIVISION REPORT FOR JUNE 1945

CLINICAL MEDICINE AND MEDICAL RESEARCH - L. O. Jacobson, Section Chief

During the past month, May 15 to June 15, 1945, 245 physical examinations were done; 61 were academic and 184 non-academic personnel. 91 pre-employment physical examinations were done; 6 individuals were rejected because of findings on clinical or laboratory examinations. During this same period 4035 clinical laboratory examinations were made. This included laboratory work on 85 new personnel, 144 controls and 595 in the work hazard group. Abnormalities considered on the basis of the white blood count showed individuals with abnormalities in this group of 33%, 46% and 45% respectively.

A comparative study on the analysis of T in tissues by means of electrometric and fluorimetric methods has shown the methods to be comparable in accuracy.

Dogs given total body x-ray as well as those given internal emitters have consistently shown a decrease in urinary coproporphyrin excretion down to as low as 20% of the average control values.

A relative increase in the ultraviolet absorption at 243 m μ and at 330 m μ has been found in the urine of irradiated dogs.

In dogs treated with plutonium (intravenous or subcutaneous injections) there appears at the end of 7 to 10 days a diminution of albumin and an increase of the α 2-globulin components. The same changes have been observed in dogs treated with lethal doses of X-rays and of Sr⁸⁹.

BIOLOGICAL RESEARCH SECTION - K. S. Cole, Section Chief

Radio-ruthenium administered by tracheal intubation to rats is absorbed and distributed much as when administered as an aerosol. At 15 days 4.5% remained in lungs, 5.6% in skeleton, 2.2% in skin, 1.5% in kidney, 1.2% in liver, 4.8% in remaining soft tissues; over 70 percent had been excreted, largely in urine.

Rats which inhaled a dose of 118 μ c of radio-yttrium aerosol lost weight rapidly and 15 out of 21 died between the 7th and 33rd days.

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The mortality at 45 days after injection of Sr⁸⁹ at 8 μ c/gm diminished in small groups of different strains of mice in the following order: black ABC > white ABC > black AF-1 > brown ABC. The MLD in all of these strains at 30 days was between 8 and 10 μ c/gm and at 45 days between 6 and 8 μ c/gm. In rats the distribution and excretion of Sr⁸⁹ was the same when injected intravenously as when injected intraperitoneally.

Six rats which have received 400 μ c of radio-yttrium by stomach tube daily for a month showed no weight loss or other observable sign of damage. One rat was given 35.7 μ c of Y⁹⁰ by stomach tube; four hours later frozen cross sections were taken for dosigraphs which gave doses of varying from 0.6 to 8.0 r/ hour to intestinal tissue.

One dog died 13 days after injection of Sr⁸⁹ at a retained dose of 1.67 μ c/g and another died 9 days after injection at a retained dose of 2.23 μ c/g. These dogs excreted 48 and 32 percent of the injected dose before death. Excretion was largely completed by three days and was greater in the feces than in the urine. Essentially all of the Sr⁸⁹ in blood was in plasma; saliva was in equilibrium with plasma. No soft tissues contained an appreciable concentration of Sr⁸⁹ but the larynx and trachea were nearly as high as teeth and bone. Clinically both dogs resembled animals given acute lethal doses of x-radiation in all respects except that hemorrhages were not as extensive.

Histological damage from 5 μ c/g of ingested radio-yttrium in rats was severe only in the colon at 3 days and recovery was complete at 8 days.

A statistical analysis shows that growth changes consequent to chronic irradiation contain two components, a rapidly accumulating and rapidly recovering component and a slowly accumulating and non-recovery component. These components are in the ratio of 3.5 to 1. The rapidly recovering component behaves like an inertial system with a transient overshoot of weight loss.

Three dogs which received 50 r daily died after accumulating 850,950 and 950 r. Their clinical behavior resembled that in dogs treated with a lethal single dose of x-radiation. Food and water consumption were low, body weight, counts of red and white cells, and the plasma MPN decreased, sedimentation rate increased. Several days before death each dog entered a terminal acute reaction of elevated temperature and heart rate, low blood pressure, zero count of leucocytes and extensive local hemorrhages.

The X/n ratio for rabbit blood responses is approximately 6.0. There are small differences between heterophils and lymphocytes.

The histological effect of 600 r on the hemopoietic tissues of rabbits, vitally stained with trypan blue and osseous iron oxide was similar to the effect of this dose on these tissues in otherwise untreated rabbits.

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Recovery in testes of rats 132 days after 600 μ varied from negligible to virtually complete. Evidence for decrease in primary ova remained inconclusive at this interval.

Mice receiving 10 μ showed no change in lymph nodes or thymus not paralleled in non-irradiated control mice.

No residual damage was evident from histopathological study of rats given a second dose of 400 μ six weeks after an original dose of 400 μ .

Pu (+4) nitrate administered by tracheal intubation killed 90 percent of rats at 1.0 μ g/g body weight, 41 percent at 0.35 μ g/g and 5 percent at 0.12 μ g/g. Lungs were enlarged, hemorrhagic, consolidated and sometimes abscessed. The white blood cell count was depressed. Only a small amount of the Pu was absorbed from the lung.

A dose of 6.2 mg (275 μ g per g body wt.) of Pu (+4) nitrate was not lethal to a mouse when given orally. The mouse became dyspnoeic, failed to eat, and was lethargic for 48 hours and lost 25 percent of its body weight within 6 days. By 15 days weight loss was 30 percent but by 20 days normal growth rate was resumed. A blood count on the fifth day was normal.

Radium decreased the red blood cell count in rats at doses from 1.0 to 0.02 μ c/g. The effect at 0.02 and 0.06 μ c/g on the red count was slight, but the dose of 0.02 μ c/g caused a 25 percent fall in white cell count. Doses of 0.125 μ c/g and above had a maximal effect upon the white cell count.

An extensive analysis of the radioautographic distribution of plutonium in mice has been made. The distribution did not follow exactly the pattern resulting from intravenous injection of India ink, vital dye, or calcium, but exhibited some features of each. With the exception of bone marrow, damage did not correlate exactly with deposition of plutonium but reflected rather the sensitivity of the various tissues.

Histological damage from plutonium in rats, mostly taken when moribund from doses of 2.0 to 0.125 μ g/g, was in general more severe than in serially sacrificed mice and involved liver, thymus, adrenals and lungs in addition to the organs previously reported as damaged in mice at 1.25 μ g/g.

MEDICAL AND INDUSTRIAL HAZARDS SECTION - J. J. Nickson, Section Chief

Routine personnel urine assay for plutonium has continued. No M I specimens with activities indicating more than two micrograms of plutonium stored in the body have been noted. During the past month there has been considerable discussion about the limits of sensitivity needed in these determinations. It has become clear that the present method must be revised to have much greater sensitivity. Work on this point is now in progress. Work on the citrate complex of plutonium indicates that no complex exists at a pH of one. On April 22nd, 6.5 micrograms of plutonium were injected into a patient

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with a diagnosis of incurable cancer at the Billings Hospital. The urinary excretion levels have been followed for almost two months. At the present time the daily rate of excretion is about 0.01% of the amount injected. Total urinary excretion is approximately 3.7% of the amount injected. A plutonium injected dog died during the past month. Analysis of the tissues show that the majority of the material is in the bone, confirming an earlier study.

2127 films from badge meter personnel monitoring devices were developed and read during the month. One total body over-exposure was noted. 4096 pocket meters were read during the month. 29 over-exposures were noted. 7 persons in the Chemistry Division were exposed to a radioactive isotope from, probably, an impurity in aluminum. Measurements of the beta and gamma activity in sputum indicated that the activity was probably present in the lungs. No symptoms have developed.

NATIONAL CANCER INSTITUTE - Egon Lorenz

LAF₁ mice of original experiment. Total chronic doses at present: (4.4 r, 2.2 r, 1.1 r and 0.11 r per 8 hours per day) 3640 r (last animal killed 6/14/45) 1820 r, 910 r and 95 r. In about 40% of the control animals the blood picture shows a lowered red count (5 to 7.5 million), with the other counts as previously reported. The picture of the experimental animals is similar. No clearcut evidence of radiation damage to the hematopoietic system is evident. Malignant lymphomas are still being found especially in the low chronic exposure groups, the acute exposure groups and the controls. These lymphomas are considered spontaneous rather than induced as they appear at approximately the same age as in the control groups. Ovarian tumors are now being found in the control group (grossly) the 0.11 r group and the 0.11 r group with an additional acute exposure of 12.5 r. These are at present considered spontaneous, while in all other groups they have to be considered induced.

Hybrid guinea pigs of original experiment. Total doses and exposure levels are the same as for mice of the original experiment. Radiation damage is now observed in the animals of the 1.1 r level also, in which a significant lowering of the platelet count is found. In the surviving animals of the 2.2 r group there is a significant lowering of all counts, in the surviving animals (5) of the 4.4 r group all counts are considerably lowered especially the platelet counts.

Inbred guinea pigs of family 2 exposed to 3.8 r per 8 hours per day. All animals were removed from the field at doses of 850 to 1000 r. All animals with a red count lower than 2.8 millions died of aplastic anemia within 2 weeks after removal from the field. Three animals with red counts of 2.3 to 2.9 millions are alive at present, 3 to 4 weeks after removal from the field. So far no recovery has been observed. This failure of recovery of the hematopoietic system might explain the findings that the lethal dose of the hybrid guinea pigs is dependant upon the total dose rather than the rate of at which the dose is administered.

Rabbits of original experiment. Total chronic doses at present: (8.8 r, 4.4 r, 2.2 r, 1.1 r, and 0.11 r) 6100 r, 3050 r, 1520 r, 760 r and 76 r. Beside the previously mentioned reversal of the differential count dependent upon total dose there is a slight lowering of the platelet count in the animals of the 8.8 r and 4.4 r groups.

A quantitative morphologic analysis of testes of mice exposed daily to 10 r of x-rays given in approximately 1 1/2 minutes, 5 times per week, revealed that the amount of interstitial tissue is not increased. It probably shows a slight decrease.

Contract # W 7405-eng-48a

A. METABOLIC STUDIES OF FISSION PRODUCTS

The soil and plant studies have been concluded for the present and a final report is being prepared. The long term aerosol studies are being continued. A special series of smoke studies appear in a separate report. A method for the isolation of Pa²³³ free from fission products, uranium, and thorium is being developed.

B. METABOLIC STUDIES OF PRODUCT

The retention of plutonium by the lungs of rats exposed to the inhalation of PuO₂ smokes was found to be approximately 5% of the originally inhaled activity, 256 days after exposure. The rate of elimination of the retained activity in the lungs at the end of the 8½ months interval was approximately 0.5% per day. The behavior of both plutonium and fission products following inhalation of PuO₂ smoke containing fission product was found to be very similar 64 days after exposure.

A patient suffering from carcinoma of the stomach, received, by intravenous injection, approximately 5 μ gms of plutonium as PuO₂(NO₃)₂, enriched with Pu²³⁸ so that the activity was equivalent to 50 μ gms of Pu²³⁹. Four days later, as a result of surgery, specimens of bone, spleen, tumor, omentum, and skin were obtained. The distribution pattern of these tissues were very similar to that observed in rats. The highest degree of deposition within the bone was present in the trabecular portion of the marrow. The rate of urine elimination was low falling below 0.01 percent per day at the end of 16 days.

A new method for the relatively rapid analysis of large specimens of urine and feces has been developed, whereby it would be possible to detect 2×10^{-6} μ gms of plutonium in each days output of urine or feces. A detailed description of this method is being forwarded to the appropriate parties in all operating areas.

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Contract # W 7405-eng-48c

BLOOD STUDIES ON TOTAL BODY IRRADIATED PATIENTS - B. V. Low-Beer

Ten of the 25 previously treated patients were studied and 2 new patients were treated. One hundred and forty-five complete blood counts and one sternal marrow study were done.

Patient No. 26 received a total of 300 r at the rate of 10 r per day on the 1000 kv x-ray machine, finishing June 19th. At that time he was in good general condition and showed only an insignificant drop in total WBC. Patient No. 27 is under treatment on the 1000 kv apparatus, receiving 10 r daily and to date shows no change.

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NATIONAL CANCER INSTITUTE REPORT FOR JUNE 1945

Drs. Lorenz, Neston, Eschenbrenner and Deringer

BIOLOGIC ACTION OF X AND GAMMA RAYS

- I. Continuous exposure for 8 hours daily
- II. Breeding experiments (continuous exposure for 8 hours and 24 hours daily)
- III. Hematology
- IV. Pathology

I. Continuous exposure for 8 hours daily. Surviving original LAF₁ mice and guinea pigs (daily doses: 4.4 r, 2.2 r, 1.1 r and 0.11 r).

Approximate total doses: 3640 r (last animal killed 6/14), 1820 r, 910 r and 95 r. (Additional acute exposures not added). Rabbits (daily doses 8.8 r, 4.4 r, 2.2 r, 1.1 r and 0.11 r). Approximate total doses: 6100 r, 3050 r, 1520 r, 760 r and 76 r (additional acute exposures not added).

Term Experiments

LAF₁ mice: (daily doses 8.8 r, 4.4 r and 1.1 r)

| | |
|------------------------------|-------------------------|
| 16 and 14 months experiment: | 1560 r, 790 r and 200 r |
| 12 and 10 months experiment: | 1160 r, 580 r and 145 r |
| 8 and 6 months experiment: | 620 r, 310 r and 80 r |
| 4 and 2 months experiment: | 300 r, 150 r and 37 r |

Inbred guinea pigs of family 2 (daily dose 8.8 r) all removed from field at doses ranging from 850 r to 1000 r).

During the month 3 of the original LAF₁ mice died and 10 were killed and autopsied due to moribund condition or tumor formation. The animals which died were distributed among the different groups as follows: 1 control male, 1 male exposed to 1.1 r and 1 female exposed to 2.2 r. The cause of death was obscure in the male animals, as all organs appeared grossly normal. The female had a small ovarian tumor, a large subcutaneous tumor and nephritic kidneys. The animals which were killed and autopsied were distributed among the different groups as follows: one control female with malignant lymphoma and an enlarged ovary (probably early ovarian tumor). One male, exposed to 12.5 r at the age of approximately 5 months with malignant lymphoma. Two females, exposed to 0.11 r: both showed one ovary enlarged (probably early ovarian tumors). One female exposed to 0.11 r and an additional acute exposure of 12.5 r, it had grossly lymphoma and a probable ovarian tumor. Two females exposed to 1.1 r and an additional acute exposure of 50 r. Both had malignant lymphoma and bilateral ovarian tumors. One male, exposed to 2.2 r with malignant lymphoma, two females, exposed to 2.2 r, one with malignant lymphoma and with an ovarian tumor, the other with

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an ovarian tumor and 2 subcutaneous tumors. One male exposed to 4.4 r (the last animal of this level) in moribund condition but without any gross lesions.

The following table gives the data on the surviving animals of the different groups.

| <u>Animal Group</u> | <u>Sex</u> | <u>Age (months)</u> | <u>Initial number</u> | <u>Survivors</u> |
|----------------------------|------------|----------------------|-----------------------|------------------|
| Control I | m | 30 1/4 | 8 | 4 |
| | f | 30 1/4 | 8 | 2 |
| Control II | m | 28 1/2 | 8 | 2 |
| | f | 28 1/2 | 8 | 1 |
| Acute exp. 12.5 r | m | 31 1/4 | 8 | 3 |
| | f | 31 1/3 | 8 | 2 |
| Acute exp. 50.0 r | m | 29 2/3 (last animal) | 8 | 0 |
| | f | 31 1/4 | 8 | 1 |
| 0.11 r | m | 30 1/4 | 8 | 3 |
| | f | 30 1/4 | 8 | 1 |
| 0.11 r + 12.5 r (acute) | m | 30 1/4 | 8 | 4 |
| | f | 30 | 8 | 4 |
| 0.11 r + 50 r (acute) | m | 30 1/4 | 8 | 1 |
| | f | 30 1/4 | 8 | 1 |
| 1.1 r | m | 28 3/4 | 8 | 1 |
| | f | 28 3/4 (last animal) | 8 | 0 |
| 1.1 r + 12.5 r(acute) | m | 26 1/2 (last animal) | 8 | 0 |
| | f | 29 | 8 | 3 |
| 1.1 r + 50 r(acute) | m | 28 3/4 | 8 | 2 |
| | f | 28 3/4 | 8 | 1 |
| 2.2 r | m | 29 | 8 | 1 |
| | f | 29 (last animal) | 8 | 0 |
| 2.2 r + 12.5 r(acute) | m | 25 1/2 (last animal) | 8 | 0 |
| | f | 29 1/4 | 8 | 1 |
| 2.2 r + 50 r(acute) | m | 28 3/4 | 8 | 1 |
| | f | 29 (last animal) | 8 | 0 |

| Animal Group | Sex | Age (months) | Initial number | Survivors |
|--------------------------------|-----|----------------------|----------------|-----------|
| 4.4 r (all groups) | m | 29 (last animal) | 24 | 0 |
| | f | 28 (last animal) | 24 | 0 |
| 8.8 r (all groups) | m | 24 1/2 (last animal) | 24 | 0 |
| | f | 24 (last animal) | 24 | 0 |
| 8.8 r (term exposure 300 r) | m | 29 1/2 | 8 | 2 |
| | f | 28 (last animal) | 8 | 0 |
| 8.4 r (term exposure 680 r) | m | 28 1/2 (last animal) | 8 | 0 |
| | f | 29 1/2 | 8 | 1 |

Data of the table are not clearcut as there exists other factors influencing the life span besides irradiation. This is evidenced by the fact that there are fewer surviving mice in the second (younger) control group. It seems that the following conclusions can be drawn: The life span of the males is not affected in the acute exposure groups, the 0.11 r groups, most likely not in the 1.1 r groups and the limited exposure group of 300 r on the 8.8 r level. In some of these groups in which the number of surviving animals is smaller than the number of the control group, there has been evidence of acute lethal infections. The life span of the females is not affected only in the 12.5 r acute exposure group, the 0.11 r group and the 0.11 r group which received in addition 12.5 r acute exposure. In all other groups including the 50 r acute exposure group there is a lowering of life span. Contributing factors to this lowering of the life span in the females may be the higher incidence of induced leukemia in comparison to the males and perhaps, also the induction of ovarian tumors.

The first ovarian tumors have been observed in the mice of the 0.11 r group, the 0.11 r group exposed in addition to 12.5 r (acute) and in one control (grossly). These tumors in the 2 groups of irradiated mice, occurring at approximately the same age as in the controls are considered at present to be spontaneous.

One guinea pig of the original series, exposed to 2.2 r to a total dose of approximately 1520 r was killed and autopsied on account of aplastic anemia (terminal R.B.C. = 300,000). It showed at autopsy the typical gross picture of patchy ecchymoses of the small intestine. So far 3 animals of this level have come to autopsy on account of aplastic anemia after having been exposed to doses corresponding roughly to the

lethal doses found for the 4.4 r and 8.8 r levels. Only 3 inbred guinea pigs of family 2 (out of 12) are alive, the others died. All were removed from the field at doses ranging from 850 to 1000 r (8.8 r level). See hematology (III). All rabbits are alive.

II. Breeding experiments

Nothing new to report.

III. Hematology

Changes in the blood counts of the control mice recently observed consist mainly in a lowering of the red count and are perhaps attributable to old age. In the nine surviving control mice of both sexes, 4 show red counts between 5 and 7.5 millions, in the remainder the red count lies between 8 and 10 millions. The white count of the controls is unchanged from that previously reported. A similar picture is found in all surviving experimental animals and there is no clearcut evidence of radiation damage to the hematopoietic system.

The blood picture of the surviving guinea pigs is as follows: Those exposed to acute exposures of 12.5 r and 50 r, those exposed to 300 r or 600 r respectively on the 8.8 r level, and those of the 0.11 r level have blood pictures comparable to that of the controls. The guinea pigs exposed to 1.1 r for 8 hours show normal blood counts with the exception of the platelet counts which lie between 200,000 and 250,000 (normal 250,000 to 300,000). The surviving guinea pigs of the 2.2 r level show red and platelet counts lowered in varying degrees, with the white count approximately normal. One guinea pig of this level which came to autopsy during the month had a drop in red count from 4.3 millions to 800,000 in 4 weeks while the platelets dropped from 44,000 to 7,700. All counts are lowered considerably in the 5 surviving guinea pigs of the 4.4 r level (total dose at present approximately 3640 r). In these animals the platelet count is considerably below 100,000.

Blood counts of the inbred guinea pigs exposed to 8.8 r to total doses of 850 to 1000 r are summarized in the table. It shows that animals with a red count of 2.8 millions at the end of the exposure will die of aplastic anemia within 2 1/2 weeks. Animals, which were removed from the field with red counts of 2.86, 2.9 and 2.35 are alive at present, 3 - 4 weeks after the termination of the exposure; in all of them the red count has continued to drop and the other counts show either little or no recovery. This apparent lack of recovery seems to explain the not very significant differences in lethal doses for the hybrid guinea pigs on the different level, i.e. the total dose in chronic exposure is apparently of greater importance than the rate of administration of the dose.

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Guinea pigs (family 2) exposed on 8.8 r/8 h level - total dose 850 to 1000 r

| Animal number | Sex | Blood counts | | | | | | | | | | | | Alive and time after end of exposure | Dead and time of death after end of exposure |
|---------------|-----|----------------------------|-----------|-----------|-------|--------------------|-----------|-----------|-------|--------------------------------|-----------|-----------|-------|--------------------------------------|--|
| | | At beginning of experiment | | | | At end of exposure | | | | At present or at time of death | | | | | |
| | | R.B.C. x 106 | W.B.C. %N | Pl. x 103 | %L | R.B.C. x 106 | W.B.C. %N | Pl. x 103 | %L | R.B.C. x 106 | W.B.C. %N | Pl. x 103 | %L | | |
| H 83 | ♂ | 6.4 | 4100 | 240 | 13 85 | 2.86 | 17.4 | 2600 | 5 94 | 1.94 | 14.3 | 1850 | 10 88 | Alive after 4 weeks | Dead after 2 weeks |
| H 84 | ♂ | 6.6 | 3700 | 260 | 36 62 | 2.82 | 11.0 | 1750 | 7 92 | 1.25 | 12.1 | 850 | 8 88 | ----- | Died while in field |
| H 85 | ♀ | 5.0 | 3200 | 260 | 30 69 | 1.45 | 11.0 | 2500 | 9 89 | -- | -- | -- | -- | ----- | Died while in field |
| H 86 | ♂ | 5.5 | 6600 | 330 | 20 77 | 1.54 | 7.7 | 350 | - 97 | -- | -- | -- | -- | ----- | Died while in field |
| H 88 | ♂ | 5.2 | 3900 | 340 | 34 65 | 1.88 | 20.9 | 1200 | 7 89 | 1.05 | 11.1 | 1700 | 5 93 | ----- | Died after 2½ weeks |
| H 90 | ♂ | 6.2 | 6100 | 260 | 28 69 | 2.85 | 20.9 | 2300 | 14 85 | 2.65 | 20.9 | 2000 | 7 89 | Alive after 3 weeks | ----- |
| H 91 | ♀ | 5.7 | 3500 | 260 | 35 62 | 2.9 | 14.3 | 1850 | 7 91 | 2.09 | 19.8 | 2300 | 5 92 | Alive after 3 weeks | ----- |
| H 92 | ♀ | 5.6 | 5100 | 230 | 27 72 | 1.24 | 16.5 | 1400 | 3 97 | 1.25 | 15.4 | 1800 | 6 90 | ----- | Died after 1 week |
| H 93 | ♀ | 4.9 | 5400 | 300 | 18 77 | 2.02 | 14.3 | 1950 | 2 97 | 1.24 | 9.9 | 1600 | 2 97 | ----- | Died after 1½ weeks |
| H 94 | ♀ | 5.9 | 6400 | 210 | 17 81 | 2.36 | 14.2 | 1900 | 3 96 | 2.18 | 7.7 | 650 | 2 98 | ----- | Died after 1 week |

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The blood picture of the rabbits shows beside the reversal of the differential count dependent upon total dose as previously reported, a lowering of the platelet count in the rabbits of the 8.8 r level (total dose approximately 6100 r) to 150,000 - 225,000 (normal 250,000 to 300,000) and to 180,000 to 200,000 in the rabbits of the 4.4 r level (total dose approximately 3050 r).

IV Pathology

Mice: Tissues have become available for histologic study on the following mice. One on the 4.4 r per 8 hours per day level (total dose approximately 3550 r), four on the 2.2 r per 8 hours per day level (total doses from approximately 1700 to 1740 r), six on the 1.1 r per 8 hours per day level (total dose from approximately 830 to 860, and four on the 0.11 r per 8 hours per day level (total dose approximately from 68 to 70 r).

Several additional lymphomas have appeared and their occurrence in relation to total dose is in keeping with the general remarks regarding the occurrence of these tumors made in recent reports.

All females exposed on the 4.4 r, 2.2 r, and 1.1 r levels have ovarian tumors. Subcutaneous sarcomas were present in 2 of 10 females. These tumors have been observed only in females, and only in those having ovarian tumors, they arise in the mammary glands. None has been observed in control animals.

Recognizable damage to spermatogenic elements of the testes are apparent only on the 8.8 r and the 4.4 r levels so far.

A quantitative morphologic analysis of testes of mice exposed daily to 10 r given in approximately 1 1/2 min., five times per week for a total dose of 300 r has been completed. This experiment was conducted to determine whether there is any change in the quantity of interstitial tissue in the testis accompanying marked damage of spermatogenic elements. The mice were LAF₁ hybrids and were 2 months of age at the start of exposure and 3 1/3 months of age when autopsied the day following the last exposure. Nine experimental and ten control animals of the same age were available for study. At autopsy the epididymus and associated fat was carefully dissected from the testes and the fresh weight of both obtained. Following fixation in Zenker-formol, washing in water, and partial dehydration in 70% alcohol for two days, each pair of testes was again weighed. The testes were imbedded in paraffin and were sectioned through their approximate maximum diameters, one being sectioned transversely and the other longitudinally. They were stained with Mallory's aniline blue with acid fuchsin as a counterstain, the latter being found to be a useful differential stain for interstitial cell cytoplasm. Using the method of Chalkley (J. Nat. Cancer Inst. 4: 47-53, 1943) one section of each testis was analyzed for

the ratio of area of interstitial cells to the area of other tissue (spermatogenic elements, connective tissue, blood vessels). The measurements were made with a 47.5 X objective and 15 X eye-piece. They were made on a series of random fields traversing the entire section and a total of 1,000 random fields were covered on each section. Measurements were done by two individuals and repeat runs showed a maximum error of 2%. The data are presented in the table, and show that interstitial tissue is certainly not increased and probably is decreased.

| Autopsy number | fresh testes (2) wt. | m. grams fixed | body wt. - grams | % testes wt. / body wt. | % testes area = interstitial T. | mgm. interstitial T. (fresh wt. calculation) | mgm. interstitial T. (fixed wt. calculation) | |
|----------------|----------------------|----------------|------------------|-------------------------|---------------------------------|--|--|----------|
| D5092 | 220 | 168 | 31 | 0.71 | 4.38 | 9.65 | 7.37 | CONTROLS |
| D5093 | 210 | 162 | 32 | 0.66 | 4.52 | 9.50 | 7.33 | |
| D5094 | 218 | 168 | 31 | 0.70 | 4.32 | 9.41 | 7.26 | |
| D5095 | 204 | 155 | 31 | 0.66 | 4.46 | 9.11 | 6.92 | |
| D5096 | 208 | 158 | 31 | 0.67 | 5.19 | 10.79 | 8.20 | |
| D5097 | 221 | 168 | 34 | 0.65 | 5.15 | 11.37 | 8.64 | |
| D5098 | 226 | 172 | 36 | 0.63 | 5.81 | 13.13 | 9.99 | |
| D5099 | 180 | 135 | 33 | 0.54 | 5.92 | 10.65 | 7.68 | |
| D5100 | 212 | 165 | 33 | 0.63 | 4.68 | 9.91 | 7.72 | |
| D5101 | 200 | 158 | 30 | 0.67 | 4.33 | 3.67 | 6.85 | |
| Average: | 210 | 161 | 32 | 0.65 | 4.88 | 10.22 | 7.83 | |
| D4841 | 94 | 81 | 29 | 0.32 | 7.84 | 7.37 | 6.35 | |
| D4842 | 90 | 72 | 27 | 0.33 | 8.53 | 7.63 | 6.14 | |
| D4843 | 86 | 71 | 27 | 0.32 | 8.63 | 7.42 | 6.12 | |
| D4844 | 72 | 53 | 28 | 0.26 | 11.31 | 8.14 | 6.56 | |
| D4845 | 91 | 76 | 28 | 0.32 | 8.21 | 7.47 | 6.24 | |
| D4846 | 114 | 91 | 29 | 0.39 | 8.50 | 9.69 | 7.73 | |
| D4847 | 100 | 79 | 27 | 0.37 | 9.33 | 9.33 | 7.37 | |
| D4848 | 88 | 73 | 27 | 0.33 | 9.39 | 8.26 | 6.85 | |
| D4849 | 91 | 74 | 29 | 0.31 | 9.21 | 8.38 | 6.81 | |
| Average: | 92 | 75 | 28 | 0.33 | 8.99 | 8.21 | 6.68 | |

With excessive damage of spermatogenic elements following irradiation, examination of a section of a testis without making measurements gives the impression that the interstitial tissue is increased. The literature on this subject is much confused, most observers feeling that there is an absolute increase of interstitial tissue, and the more conservative suggesting that this apparent increase may be only relative and not absolute. None appears to have considered a decrease in interstitial tissue. This experiment is being repeated but with an exposure of the mice to a total dose of 600 r, the results of which will be reported at a later date.

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Report for June 1945

TECHNICAL PROGRESS REPORT ON THE METABOLIC STUDIES OF PLUTONIUM

Joseph G. Hamilton

1. Radioautographic Studies

Additional bone radioautographs, including samples from a rib of a human subject, are in various states of preparation. A large series of specimens from animals subjected to the decalcification-calcification cycle of treatment will soon be available for radioautographic study.

2. Tracer Studies

The two animals exposed to PuO_2 smoke were sacrificed 256 days later and the results obtained with these two animals appear below. More animals exposed both to PuO_2 smokes and $\text{PuO}_2(\text{NO}_3)_2$ aerosols are being carried along. Since with only two animals, these results can only be considered qualitative in character.

TABLE I

The Percent Distribution of Plutonium in Two Rats 256 Days After Inhalation of PuO_2 Smoke

| <u>Tissue</u> | <u>Rat #1</u> | <u>Rat #2</u> | <u>Average</u> |
|---------------|---------------|---------------|----------------|
| Lungs | 6.18 | 3.38 | 4.78 |
| Liver | .014 | .042 | .028 |
| Kidney | .0015 | .0005 | .001 |
| Spleen | .0023 | .0039 | .0031 |
| G. I. | .022 | .0070 | .015 |
| Head | <.05 | <.05 | <.05 |
| Skeleton | .16 | <.20 | <.20 |
| Balance | .032 | .014 | .023 |
| Urine | 2.34 | 2.42 | 2.38 |
| Feces | 91.2 | 93.8 | 92.5 |

In Table II there is presented the rate of excretion per day of the activity remaining in the animals at the indicated time intervals.

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TABLE II

The percent Excretion of Retained Plutonium From the Rats at the Indicated Time Intervals.

| Day | Total Excretion Per Day* | Lung Activity* | Percent Excreted Per Day |
|---------------|--------------------------|----------------|--------------------------|
| 8 (4-16) | 139.9 | 2604 | 5.25% |
| 16 (8-24) | 59.5 | 1896 | 3.14% |
| 32 (24-40) | 11.9 | 1531 | .78% |
| 64 (40-80) | 10.77 | 1244 | .87% |
| 96 (72-112) | 7.53 | 918 | .82% |
| 128 (108-144) | 7.20 | 737 | .98% |
| 192 (144-224) | 2.47 | 446 | .55% |
| 256 (200-256) | 1.29 | 362 | .36% |

*Indicated as the average number of counts per second for the two animals.

The three most significant facts to be noted in this experiment are as follows: First, a very significant amount of the originally inhaled PuO_2 is retained by the lungs after eight and one-half months in the rat. Second, there is only a very slight degree of absorption from the lungs, with deposition in other tissues. Third, a very significant rate of loss of material from the lungs continued at a diminishing rate for the 256 day interval. More precise evaluation of the values for lung retention and rates of excretion at this prolonged interval will be available later. However, I doubt if the present figures for the rat will have to be revised at that time by more than a factor of two.

The results are now available from a group of three rats sacrificed 64 days following exposure to PuO_2 smoke prepared from neutron irradiation plutonium metal and the salient facts are summarized in the following table.

TABLE III

The Distribution of Plutonium and Long-lived Fission Products in the Same Rats 64 Days after Exposure to PuO_2 Smoke Prepared from Neutron Irradiated Plutonium Metal.

| Tissue | Plutonium | Fission Products |
|-------------|-----------|------------------|
| Lungs | 8.38% | 9.51% |
| Liver | < .01% | .028% |
| Kidney | < .01% | .033% |
| G. I. Tract | .09% | .088% |
| Spleen | < .01% | .014% |
| Head | < .20% | .20% |
| Skeleton | < .50% | .27% |
| Balance | < .20% | .12% |
| Urine | 1.20% | 3.09% |
| Feces | 90.40% | 87.60% |

It is interesting to compare these results with the corresponding data for the 0, 4, and 16 day intervals which appear in the April 1945 Monthly Report. One inconsistency appears in the relatively lower skeleton values at the 64 day interval for fission product deposition. Otherwise the pattern is consistent and the distribution of the two types of active material remained quite similar. The rates of excretion (chiefly lung activity) per day were .29% for plutonium and 1.90% for fission products of the corresponding material remaining in the body at the end of the 64 day interval. The plutonium excretion rate, at the same interval, was greater in the other experiments noted above. Those figures in Table III indicate the similarity between the two types of active material but certain qualitative differences, such as the greater degree of absorption through the lungs, and the more rapid excretion of the fission products are evident.

Longer term animals exposed to this type of PuO₂ smoke are on hand and will be sacrificed at the appropriate intervals.

May 14, 1945, a human subject, suffering from a carcinoma of the stomach, received approximately 5 μ gm of plutonium as PuO₂(NO₃)₂ by intravenous injection in a solution of isotonic NaCl at pH 4. This sample of plutonium contained sufficient Pu²³⁸ to increase the specific activity of the injected material to the equivalent of 50 μ gms of Pu²³⁹. Four days later, the patient was operated upon and specimens of rib, spleen, tumor, omentum, subcutaneous tissue, and skin were obtained. At the same time, a sample of blood was also secured. Unfortunately, the surgeon failed to secure a specimen of liver. The patient is a 50 year old male, weighs 58.1 kilograms, and is in good general physical condition, aside from the tumor. All excreta has been collected at daily intervals since the time of injection of the plutonium.

The content of plutonium in the different tissues in terms of percent of the administered dose is given in the following table together with the excretion per day. Due to the surgical procedure, the patient was on a very restricted diet with the result that for the first two and one-half weeks, little fecal elimination took place. The per organ content of skeleton and blood were taken on the basis of these structures, representing 15% and 10% respectively of the patient's weight. The sample of rib was carefully slit open, the marrow removed by gentle washing with normal saline and then the trabecular bone and endosteum were scraped away from the cortex. The periosteum was likewise removed from the cortical bone and all four components assayed for their plutonium content.

The relatively high content of plutonium in the separated trabecular material from the specimen of rib, which also contained the endosteal tissue, is correlated with the radioautographic studies in animals. It will be recalled that bone radioautographs showed the bulk of the plutonium to be concentrated in the endosteal region and about the trabecular bone. The relatively low values for cortical bone and periosteum likewise follow the pattern indicated by the animal studies. However, the

high plutonium content of the marrow in man was surprising since no indication of this fact was evident from our animal studies. The possibility of entrapment of plutonium in the colloidal state by the phagocytic cells in the marrow is ruled out in our opinion for two reasons. First, animal studies done concurrently by intravenous injection of aliquots from the same solution of plutonium given to the patient showed no excessively high concentration in either the liver or the spleen. When the material is colloidal in character, very high uptake values for these two organs have been consistently observed. Second, the plutonium content of the spleen of the patient was quite low. The possibility of leaching of the plutonium from the endosteum, when the marrow was washed out from the bone, is very unlikely due to the fact that under the far more rigorous conditions surrounding decalcification of bone with dilute acid, very little leaching takes place. We have not received radioautographs from rats receiving plutonium by intravenous injection and further more, all bone radioautographs available at present from Berkeley have been from animals that had received the material two months or longer before they were sacrificed. During this interval, the plutonium may have migrated from the marrow to the trabecular bone and the endosteum. Because of these two gaps in the picture, we cannot state that under the conditions of this human study, the same type of marrow concentration does not exist in the rat. We are now going to secure bone radioautographs from rats under comparable conditions in an attempt to settle this point.

TABLE IV

The Distribution of Approximately 5 μ gms of Plutonium in a Human Patient, 4 Days Following the Intravenous Administration of the Material as $\text{PuO}_2(\text{NO}_3)_2$. The Excretion Data for the First 18 Days Following Administration is Included.

| | <u>% per Organ</u> | <u>% per gram</u> |
|---------------------|--------------------|-------------------|
| Cortex | | .0072 |
| Marrow | | .019 |
| Spicules | | .032 |
| Periosteum | | .0048 |
| Whole Bone | 87.2 | .010 |
| Spleen | .22 | .0019 |
| Tumor | | .0011 |
| Omentum | | .00043 |
| Skin | | .00048 |
| Subcutaneous Tissue | | .00037 |
| Blood | 7.49 | .0013 |
| Plasma | | .0023 |
| RBC | | .00028 |

Excretion Data

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|-------|-----|-----|-----|------|------|------|------|------|-------|------|------|
| Urine | .48 | .15 | .12 | .031 | .037 | .014 | .014 | .016 | .069 | .026 | .036 |
| Feces | | | | .31 | | | | | .0092 | | |

| | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|-------|------|------|------|------|------|-------|------|-------|
| Urine | .029 | .017 | .017 | .013 | .016 | .0056 | .010 | .0062 |
| Feces | | | | | | | .017 | .010 |

The human excretion data indicates that the rate of urinary elimination is almost the same for rats given a portion of the same solution of plutonium, see Table V.

TABLE V

A Comparison of the Rates of Excretion of Plutonium in the Rat and Man Following the Intravenous Administration of $\text{PuO}_2(\text{NO}_3)_2$

| Day | <u>RAT</u> | | <u>MAN</u> | |
|--------|----------------|-------|----------------|---------|
| | % Dose per Day | | % Dose per Day | |
| | Urine | Feces | Urine | Feces |
| 0 - 1 | .32% | 1.39% | .48% | .076% |
| 0 - 2 | .15% | 2.83% | .15% | |
| 2 - 3 | .061% | 1.54% | .12% | |
| 3 - 4 | .033% | 1.92% | .031% | |
| 5 - 8 | .023% | 1.35% | .020% | .0026%* |
| 9 - 16 | .031% | ----- | .028% | |

* Also includes feces through 19 days.

The fecal excretion in the patient was far less but perhaps is related to his operation and subsequent lack of fecal output. More specimens will have to be accumulated before any conclusive opinion can be reached in regard to the rate of fecal excretion of plutonium by this patient.

It is planned to continue the daily collections of both urine and feces from this patient for an indefinite period. In addition, there is enough Pu for another human study when a suitable patient is available.

[REDACTED]

It should be pointed out that we feel the use of Pu²³⁸ as a tracer for a limited number of selected patients is desirable since it is possible to use from 1 to 5 μ gms of plutonium, which is the range of dosage in man that is of greatest interest, due to the high specific activity of this material.

Mr. Scott has recently developed a method for the reasonably rapid and quantitative extraction of plutonium from 24 hour collections of both urine and feces. The material is ashed and then the plutonium extracted from the ash by means of Hexone. From 75% to 80% recovery has been consistently obtained. The entire procedure of ashing, extraction, and counting can be done with an average expenditure of 2 hours per sample, providing adequate facilities for ashing are available. This method is readily adapted to handling up to ten days accumulation of urine. The final precipitate is mounted on platinum dishes 5 centimeters in diameter to reduce self-absorption but even under these conditions our background of the counter is approximately one count per minute. On the basis of using 10 day urine samples, it should be possible to detect a daily excretion of 2×10^{-6} μ gms per day. Difficulty of securing alpha particle free reagents, particularly zirconium and lanthanum, presents a serious problem and must be kept in mind. Mackay's lanthanum and zirconium are particularly bad in this respect. The alpha activity from these reagents follows very closely the chemistry of plutonium in this type of separation.

Our work with plutonium has been greatly facilitated by the extensive cooperation given to us by different members of Doctor Latimer's group and in particular, by Doctor Connick who supervised the preparation of the sample of Pu²³⁸ and assisted Mr. Scott in developing his method for assaying large samples of urine and feces.

3. Decontamination Studies

Preliminary results indicate that the technique of overlaying the endosteal region of the bone by the decalcification-calcification cycle, described in an earlier report may be successful. Additional data to either substantiate or deny this most hopeful procedure will shortly be available.

4. Soil Studies

Experiments were conducted to determine the degree of fixation of product in its three valence states, on clay. For preliminary experiments, a hydrogen clay (Death Valley Bentonite) was suspended in distilled water at pH 4.5. Although product in the +3 and +4 states tends to precipitate at the hydrogen ion concentrations used, it is believed that the data nonetheless show pronounced adsorption of these states on the clay. The percentage adsorption of the three valence states on hydrogen clay suspensions of various strengths is given in the following table:

| Percent Conc. of Clay | Percent Fixation of +3 | Percent Fixation of +4 | Percent Fixation of +6 |
|--------------------------|---------------------------|---------------------------|---------------------------|
| .01 | 94.2 | 66.0 | 18.6 |
| .05 | 98.5 | 94.5 | 68.0 |
| .10 | 98.7 | --- | 95.0 |
| .50 | 99.0 | --- | 99.1 |
| 1.00 | 99.3 | --- | 99.4 |

Additional experiments are being carried out to determine the fixation of product on clay under conditions of greater acidity and electrolyte concentration. It is of interest to note that a pronounced difference in the behavior of +3 and +6 plutonium exists in the higher dilutions of clay which then vanishes at the higher clay concentrations. The lower affinity of clay for +6 plutonium is probably due to the fact that +6 plutonium exists in solution as the plutonyl (PuO_2^{++}) ion while in the +3 state, it exists as Pu^{+++} . The affinity of clay for cations is proportional to the number of positive charges carried by the ions in solution.

Experiments are in progress to ascertain the availability of the three valence states of plutonium to plants.

5. Projected Studies

The tracer, soil, plant, smoke, radioautographic and human studies are to be continued for the next two months.