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| Iowa State College | 41 |
| Los Alamos | 42-44 |
| Madison Square Area | 45 |
| Massachusetts Institute of Technology | 46 |
| Monsanto Chemical Company, Dayton | 47 |
| National Bureau of Standards | 48 |
| Patent Advisor | 49 |
| Research Division (for NEPA), Oak Ridge | 50 |
| Research Division, Oak Ridge | 51-65 |
| University of California Radiation Laboratory | |
| Information Division | 66-69 |
| E. O. Lawrence | 70 |
| Patent Department | 71 |
| J. G. Hamilton | 72 |
| J. H. Lawrence | 73-74 |
| R. L. Dobson | 75 |
| N. Garden | 76 |
| R. S. Stone | 77 |
| University of Rochester | 78 |

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1175103

TABLE OF CONTENTS

DECLASSIFIED

I THE METABOLIC PROPERTIES OF PLUTONIUM AND ALLIED MATERIALS

Radioautographic Studies 4
Tracer Studies 5
Decontamination Studies 16
Radio-Chemical Isolation 21

II BIOLOGICAL STUDIES OF RADIATION EFFECTS

Lethal Effects on Mice of Fast Neutrons from the 184-inch Cyclotron 24
Lethal Effects on Mice of 180 Mev Deuterons from the 184-inch Cyclotron 25
Rate of Metabolism of $CO_2$ 26
Further Experiments Concerning the Biological Effects Due to Uranium Fission 27

III BIOLOGICAL EFFECTS OF RADIATION FROM EXTERNAL AND INTERNAL ZONES

Administration 34
Hematological Effects of Total Body Irradiation from External and Internal Sources 35
Metabolism and Effects of Radio-Iodine ($I^{131}$) 37

IV HEALTH CHEMISTRY 53

1175104

# I. THE METABOLIC PROPERTIES OF PLUTONIUM AND ALLIED MATERIALS

J. G. Hamilton

## Radioautographic Studies

Radioautographic studies with the long-lived rare earths and the actinide elements are continuing with particular reference to the use of alpha particles emulsions for those radio-elements that emit this type of radiation. Considerable progress has been made toward developing a satisfactory technique for mounting the sections directly upon the emulsion. There is still difficulty in both the staining of the section and the concurrent staining of the emulsion. The successful application of this procedure should make it possible to correlate the deposition of the alpha active actinide elements with the specific cells that accumulate these substances. Moderately satisfactory radioautographs of americium from undecalcified bone sections have been obtained which corroborate the observations made earlier by the more conventional techniques. This radio-element shows a rather surprising degree of accumulation in the regions of the blood vessels within the mineralized structure of the bone.

The radioautographic studies for the long-lived fission products and the actinide elements are being continued. Preliminary radioautographic studies of the deposition of $Ac^{227}$ in bone indicate that this element is deposited in bone very much in the same pattern as has been observed with the lanthanide rare earths, americium, and curium. In order to secure the pattern of distribution more accurately, it will be necessary to age the bone sections for another 60 days so that full equilibrium may be established with the radioactive descendants of $Ac^{227}$. The necessity for this wait becomes apparent when it is recalled that radio-actinium ($Th^{227}$) has a half-life of 18.9 days and AcX ($Ra^{223}$) has a half-life of 11.2 days. Inasmuch as only 30 days had elapsed from the time of the administration of the radio-actinium to the preparation of the radio-autographs, it is apparent that a considerable fraction of the activity in the bone arose from the radio-thorium and AcX present in the solution of actinium at the time of its administration. Since we already know that the patterns of distribution in bone of both radium and thorium differ from one another, as well as from the lanthanide rare earths, americium, and curium, it will be necessary to wait until all of the activity from the radio-thorium and AcX present at the time of administration has decayed. A less significant but possible source of error is that the radio-thorium and AcX formed from the decay of actinium between the interval of administration and sacrifice of the animals may be subject to translocation. The possibility of this effect may be avoided by simply adding to the waiting period, indicated above, the interval of time between the date of administration and date of sacrifice.

1175105

The radioautographic studies with columbium have been set up. It is with particular interest that we look forward to the results of these experiments, for it might be recalled that columbium, while deposited in the skeleton to a considerable degree, is not retained as tenaciously by that organ as yttrium, zirconium, the lanthanide elements, and the actinide elements studied.

In connection with these radioautographic studies Miss Axelrod has completed a very extensive review of the field of radioautography. This material has been declassified and was presented by invitation at the Biological Chemistry Section of the American Chemical Society in New York in September of 1947.

## Tracer Studies

Radio-Silver. Tracer studies with carrier-free radioactive silver have been carried out on animals that had been subjected to ligation of the bile duct. A summary of the results are noted in Table I. It will be seen that the distribution pattern of radio-silver in those animals subjected to bile duct ligation is very different from those of the normal control animals. It would appear from the high content of the various tissues of the body, notably the liver, that this element is excreted in the carrier-free state by way of the bile.

It has been observed with carrier-free radio-silver that in blood most of the silver is bound to the serum proteins. This was found both in the in vivo and in vitro studies. If carrier-free radio-silver is added to heparinized whole blood and allowed to stand for three hours in vitro, 64 percent of the activity is in the globulin fraction, 16 percent in the albumin, and 20 percent in the red blood cell fraction. Approximately a third of the total red cell activity was in the hemoglobin. The globulin and albumin fractions were separated by the use of one-half saturated ammonium sulfate. The protein-free fraction of the serum, which was obtained by the addition of saturated ammonium sulfate to remove the albumin, contained less than 0.1 percent of the radio-silver present in the blood. It was found that the carrier-free radio-silver, as Ag ion, after its addition to blood in vitro, did not dialyze through a celloidin membrane, which suggested the possibility of its chemical combination with the protein.

The in vivo experiments were done as follows. Carrier-free radio-silver was administered intravenously and five minutes later, blood was removed and the fractionations made in the manner indicated above: 50 percent of the activity was in the globulin fraction, 32 percent in the albumin, 10 percent in red blood cells and less than 1 percent in the protein free fraction of the plasma. If is of interest to note that in this five minute interval, the liver had removed 86 percent of the total mount of radio-silver that was administered. In an additional experiment a preparation of purified rat globulin, to which radio-silver had been added, was administered by intravenous injection and the distribution of the activity in

1175106

TABLE I

A COMPARISON OF THE METABOLISM OF CARRIER FREE RADIO SILVER ($Ag^{110}$) FOLLOWING INTRAMUSCULAR ADMINISTRATION IN NORMAL RATS AND RATS AFTER LIGATION OF THE BILE DUCT

| | Bile Duct Ligated Animals | | | | Normal Controls | | | |
|---|---|---|---|---|---|---|---|---|
| | 2 Days (3 rats) | | 7 Days (3 rats) | | 1 Day (3 rats) | | 4 Days (3 rats) | |
| Tissue | % per organ | % per grams | % per organ | % per gram | % per organ | % per gram | % per organ | % per gram |
| Heart & Lungs | 1.05 | .35 | .56 | .17 | .19 | .14 | .046 | .015 |
| Spleen | -- | -- | 1.29 | .75 | .11 | .12 | .004 | .004 |
| Blood | 10.8 | .70 | 5.96 | .45 | 4.06 | .297 | .849 | .066 |
| Liver | 57.6 | 5.37 | 48.3 | 4.21 | 2.78 | .308 | 1.28 | .158 |
| Kidney | 5.67 | 2.64 | 6.56 | 2.81 | 1.27 | .631 | 2.80 | .159 |
| Brain | .12 | .078 | .037 | .022 | .038 | .029 | .019 | .019 |
| G.I. Tract | 5.10 | .28 | 2.46 | .15 | 21.0 | 2.3 | 2.37 | .09 |
| Bone | 3.33 | .17 | 4.07 | .15 | 4.22 | .162 | .660 | .007 |
| Muscle | 2.40 | .021 | 1.53 | .014 | 2.21 | .022 | 2.32 | .002 |
| Skin | 4.08 | .11 | 2.27 | .067 | 1.93 | .058 | .609 | .022 |
| Urine | 3.03 | -- | 7.96 | -- | .00 | -- | .000 | -- |
| Feces | 6.85 | -- | 18.8 | -- | 60.9 | -- | 91.74 | -- |

1175107

the blood between the globulin, albumin, and red blood cells was 76 percent, 18 percent, and 6 percent respectively, three hours after administration. Of the total dose given, 80 percent was in the liver, and 15 percent in the digestive tract, presumably having been released via the bile by the liver.

It would appear that the distribution of silver between the protein and cellular constituents of the blood are in dynamic equilibrium with each other and this very possibly is mediated by the liver. Another experiment indicated that a light chloroform anesthesia for an hour in the rat will markedly delay the excretion of radio-silver, presumably as the result of liver damage. This effect is of a reversible character since if the animals so treated are allowed to recover for a period of from four to six days after the chloroform anesthesia, the apparent ability of the liver to excrete radio-silver returns to normal.

Radio-Indium. Studies have been carried out on the distribution of carrier-free radio-indium. In Table II is presented the results found 4 and 16 days after administration of the element. It will be seen in the case of radio-indium that considerable deposition takes place in the liver, skeleton, and skin. The rather high uptake in the muscle is presumably related to the large mass of this structure. The highest concentration of radio-indium on a per gram wet weight basis is to be noted for the spleen, liver, and kidney. Bone and the majority of the soft tissues, with the exception of the brain, have comparable amounts of indium present at the 4 day interval. At the 16 day interval, the highest concentration of the indium is still present in the liver, kidney, and spleen but there has been a significant decrease at this later time period. An appreciable decrease is noted in the skeleton and all of the other soft tissues. Elimination is primarily by way of the feces. This, together with the rather high concentration in the liver, suggests the possibility that the bile may be the chief route of excretion of this element. A negligible amount of absorption takes place following stomach tube administration. It is not possible to do more with the data in hand than assume the lower limit for the absorption and this value is 0.1 percent of the administered dose.

The most noteworthy findings from the 64 day radio-indium studies is the continued and relatively high value of the accumulation in the pancreas which is actually significantly higher than that at the 16 day interval. There does not seem to be any obvious source of error to make this observation false, but its explanation is difficult. The concentration in other endocrine organs, notably adrenals, thyroid, testes, appears to remain rather high. Due to the small size of the adrenals and thyroid, these observations should be taken as a qualitative rather than quantitative indication. They are of sufficient interest that it is desirable to repeat these studies at a higher dosage level in order to establish the point definitely. If it is true that these endocrine organs show this constant pattern of selective localization, some

1175108

TABLE II

THE DISTRIBUTION OF CARRIER FREE RADIO-INDIUM IN THE RAT FOLLOWING INTRAMUSCULAR ADMINISTRATION

| | 4 DAYS | | 16 DAYS | |
|---|---|---|---|---|
| Tissue | % per organ | % per gram | % per organ | % per gram |
| Heart | .19 | .19 | .10 | .12 |
| Lungs | .56 | .37 | .54 | .34 |
| Spleen | 1.49 | 1.84 | 1.33 | 1.55 |
| Blood | 2.96 | .19 | .80 | .05 |
| Liver | 13.96 | 1.56 | 6.69 | .95 |
| Kidney | 3.57 | 1.51 | 2.46 | 1.47 |
| Adrenals | .02 | -- | .08 | -- |
| Thyroid | 0 | 0 | .04 | -- |
| Lymph Gland | .04 | -- | .04 | -- |
| Pancreas | .25 | .25 | .20 | .27 |
| Brain | .04 | .02 | .07 | .04 |
| Fat | .54 | .30 | .15 | .16 |
| G. I. Tract | 5.95 | 1.09 | 3.07 | .19 |
| Skeleton | 16.85 | .46 | 11.46 | .24 |
| Muscle | 14.71 | .12 | 11.83 | .11 |
| Skin | 17.86 | .42 | 16.38 | .45 |
| Eyes | .02 | .04 | | |
| Pituitary | 0 | 0 | | |
| Gonads | 1.12 | .32 | .82 | .30 |
| Urine | .63 | -- | 4.19 | -- |
| Feces | 19.25 | -- | | -- |
| | 99.99 | | 100.00 | |

1175109

interesting considerations are immediately apparent. The fraction of radio-indium absorbed following administration by stomach tube is less than .2 percent of the administered dose under the conditions of these experiments, and therefore it may be concluded that carrier free radio-indium in the form In $Cl_3$ shows negligible absorption from the digestive tract.

Radio-Tin. The 1 day intramuscular studies with radio-tin have been completed. This carrier-free radio-element is absorbed with considerable difficulty from the site of injection, there being nearly 85 percent of the administered dose still remaining at the site of injection at the end of 24 hours. Of the fraction absorbed during this interval, 58 percent is excreted, principally by way of the urine, 25 percent deposited in the skeleton, 5 percent in the kidneys, 6 percent in the muscle, and 4 percent in the skin. The remaining tissues show no very striking degree of uptake.

Curium. The 256 day curium studies have been completed and the data summarized in Table III. It will be seen that the per gram content in the soft tissues is quite low and that the concentration in the skeleton still remains high. In fact, the apparent concentration in the skeleton has not been altered to a measurable degree throughout the entire interval of these studies, for the bone uptake at one day after intramuscular injection has been found to lie in the range of from 18 percent to 24 percent and in this 256 day experiment there is 22 percent of the material still in the skeleton. It appears probable from these data that the excretion of curium accumulated in the skeleton precedes at the same extremely low level previously observed for plutonium and americium.

Radio-Cadinium. The one day intramuscular studies with carrier-free radio-cadium as shown in Table IV that this element is stored in the liver to a remarkable degree, approximatley 80 percent of the dose absorbed 1 day following injection having been concentrated in this organ. The content in the other tissues was not particularly striking with the possible exception of rather high level in the adrenals, the pancreas, and the ovaries. Inasmuch as the ovaries and adrenals are small structures in the rat, the total activity present was low. For this reason the values given for these two organs should be considered of qualitative rather than quantitative accuracy. The four day studies showed that the high content in the liver, kidney, and pancreas still persisted, nearly 75 percent being present in the liver at this time. Stomach tube experiments at 8 days showed that .25 percent had been absorbed from the digestive tract. This is not an upper limit but is a measured value of quantitative significance. The liver content at 15 day was 74 percent while at 64 days was well over 50 percent. The high concentration in the liver does not seem to be the result of simple entrapment by the reticulo-endothelial system in view of the fact that the per gram content in the spleen is roughly 1/25th of the concentration in the liver. In addition, only a small fraction of the cadmium remains unabsorbed at the site of injection, which suggests that this substance is fairly well mobilized and distributed throughout the body by the circulation in some soluble form for its eventual deposition and retention by the liver. Of the other soft

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TABLE III

A SUMMARY OF THE DISTRIBUTION OF CURIUM ($Cm^{242}$)
IN THE RAT 256 DAYS AFTER INTRAMUSCULAR ADMINISTRATION
AS $CmCl_3$

| Tissue | % per organ | % per gram |
|---|---|---|
| Heart and lungs | .094 | .020 |
| Spleen | .11 | .17 |
| Blood | .035 | .001 |
| Liver | 1.09 | .12 |
| Kidney | .47 | .22 |
| G. I. Tract | .083 | .002 |
| Bone | 22.0 | 1.36 |
| Muscle | .47 | .003 |
| Skin | .090 | .003 |
| Urine | 6.03 | |
| Feces | 69.5 | |

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TABLE IV

THE DISTRIBUTION OF CARRIER FREE RADIO-CADMIUM IN THE RAT FOLLOWING INTRAMUSCULAR ADMINISTRATION

| | 1 DAY | |
|---|---|---|
| Tissue | % per organ | % per gram |
| Heart | .244 | .338 |
| Lungs | .226 | .013 |
| Spleen | .244 | .451 |
| Blood | .271 | .021 |
| Liver | 77.80 | 10.19 |
| Kidney | 3.93 | 2.50 |
| Adrenals | .049 | .958 |
| Thyroid | .011 | .376 |
| Lymph Glands | .053 | .489 |
| Pancreas | .771 | .977 |
| Brain | .019 | .011 |
| Fat | .021 | .041 |
| Teeth | .019 | .147 |
| Stomach | .432 | .301 |
| Small Intestine | 4.23 | .639 |
| Large Intestine | 2.50 | .564 |
| Bone | 2.42 | .015 |
| Muscle | 1.00 | .011 |
| Skin | 2.50 | .092 |
| Ovaries | .073 | .714 |
| Pituitary | .008 | --- |
| Eyes | .011 | .038 |
| Urine | .207 | --- |
| Feces | 2.95 | --- |
| | 99.99 | |

1175112

tissues, the pancreas contains quite a concentration per gram wet weight of the carrier-free radio-cadmium, it being exceeded only by the liver and kidneys. It is of interest to note that the skeleton accumulates very little of this element, bone being less active on a per unit weight basis than all of the 20 tissues studied with the exception of heart, muscle, brain, fat, and skin. Excretion of carrier-free radio-cadmium is quite slow and most of the elimination still continues by way of the digestive tract. Very possibly, elimination is by way of the bile although as yet this point can only be speculative. Experiments are now in progress to see the effect of small amounts of carrier to determine if the presence of inert cadmium may alter the over-all metabolic picture of the distribution of this substance.

Radio-Antimony. Table V summarizes the results of the one and four day intramuscular studies with carrier-free radio-antimony. It is seen that this element is retained in the body to a rather minimal degree. Approximately 95 percent of the dose absorbed one day following intramuscular injection was eliminated, most of the antimony being excreted by way of the kidneys. The highest concentration per organ, as well as per gram, at both time intervals was found to be in the blood. After 15 days it was found that the only tissues containing accurately measurable quantities was the blood and skeleton. The average content in the blood was 1.5 percent as contrasted to 2 percent in the 4 day interval. In other words, release of this radio-element from the blood appears to be very slow. This phenoneme is strongly reminiscent of the behavior of arsenic in the rat with the exception of the fact that there is roughly 20 times as much carrier-free radio-arsenic deposited in the blood as compared to carrier-free radio-antimony. After 32 days it was found that approximately 98 percent of the radio-antimony had been eliminated, chiefly by way of the kidneys. Most of the antimony remaining unexcreted was present in the blood, there being approximately 1.3 percent of the administered dose present in the blood after this time interval.

It is planned to prepare and administer much higher levels of radio-antimony in a carrier-free state in order to secure enough activity in the other tissues to permit accurate determinations of their content of this fission product. The interpretation of the 8 day stomach tube experiments with radio-antimony is rendered difficult due to the fact that even if a large share of the antimony were absorbed, it would be excreted within a very short time and thus not appear in the various tissues. However, it is apparent that an upper level of oral absorption of from 2 to 3 percent may be set. The explanation for this is that the parenteral administration of carrier-free radio-antimony is followed by excretion primarily in the urine, the ratio of excretion between the kidneys and the digestive tract being approximately 5 to 1. Inasmuch as 97 percent of the material administered by stomach tube appeared in the feces and only 3 percent in the urine, the absorption from the digestive tract would appear to be less than 3 percent. A more quantitative evaluation of this point can only be accomplished by the administration of from 10 to 100 times the dose of

1175113

TABLE V

THE DISTRIBUTION OF CARRIER FREE RADIO-ANTIMONY IN THE RAT FOLLOWING INTRAMUSCULAR ADMINISTRATION

| Tissue | % per organ | % per gram | % per organ | % per gram |
|---|---|---|---|---|
| Heart | .016 | .022 | .007 | .007 |
| Lungs | .304 | .103 | .239 | .158 |
| Spleen | .027 | .044 | .026 | .036 |
| Blood | 1.91 | .133 | 2.04 | .128 |
| Liver | .221 | .027 | .120 | .012 |
| Kidney | .123 | .074 | .065 | .032 |
| Adrenals | 0 | 0 | 0 | 0 |
| Thyroid | .003 | --- | 0 | --- |
| Lymph Gland | 0 | 0 | 0 | 0 |
| Pancreas | .004 | .003 | .006 | .005 |
| Brain | 0 | 0 | .005 | .004 |
| Fat | .001 | .001 | .001 | .001 |
| Stomach | .016 | .008 | 0 | 0 |
| Sm Intestine | .071 | .009 | .030 | .004 |
| Lg Intestine | .142 | .030 | .019 | .002 |
| Bone | .784 | .053 | .913 | .034 |
| Muscle | .140 | .001 | .108 | .001 |
| Skin | .133 | .004 | .087 | .002 |
| Pituitary | 0 | --- | .002 | --- |
| Eyes | 0 | 0 | .005 | .015 |
| Gonads | .005 | .004 | .004 | .001 |
| Urine | 80.68 | --- | 77.45 | --- |
| Feces | 15.42 | --- | 18.86 | --- |
| | 100.00 | | 100.00 | |

1175114

radio-antimony employed, which is still below the level we feel will produce either local radiation damage to the digestive tract or generalized radiation injury to the rest of the body. The major obstacle to be noted following both parenteral and stomach tube administration with larger doses of radio-antimony arises from the quite formidable radio-chemical procedures necessary to isolate this material in the carrier-free state with an adequate degree of radio-chemical purity from the deuteron bombarded tin target.

Technetium. The volatile nature of a large proportion of the compounds of technetium has presented some most serious obstacles in the assay work with this substance. Many techniques have been explored including several types of distillation procedures as well as wet ashing of the tissues followed by co-precipitation of the technetium with gold and platinum sulfides. It would appear that the distillation technique offers the greatest promise of any of the analytical methods employed thus far, although it has the profound disadvantage of being a very laborious and time consuming method. The co-precipitation technique runs into difficulty, since it is necessary to subject the tissues to preliminary wet ashing. It is at this point that the excessive loss of the technetium takes place.

In order to circumvent these limitations, short term experiments have been done using the 110 hour technetium isotope that emits 50 killivolts gamma rays. The distribution of technetium in the tissues and excreta was measured by counting directly the gamma ray activity of the wet specimens, precautions being taken to exclude any beta rays or conversion electrons by means of aluminum filters. The incomplete results indicate that this radio-element is excreted following intramuscular administration in the rat with an extraordinary degree of rapidity, there being approximately 95 percent eliminated within 24 hours, with the kidneys acting as the principal channel of excretion.

Radio-Actinium. The 1 day radio-actinium tracer studies have been completed insofar as ashing the samples is concerned. The activity was measured together with that of the beta radiation from the short-lived descendants of AcX. It should be pointed out that these data can only be viewed at present as being of qualitative significance inasmuch as the equilibrium levels have not been established for the various descendants of the actinium. These measurements were made approximately one month after the time that the actinium solution was administered which contained equilibrium amounts of radio-actinium and actinium X. The proportion of radioactivity administered that was accumulated by the liver was found at the time of the measurements to be approximately 30 percent, and the corresponding value for bone was 34.5 percent. Although at the moment a precise calculation of what fraction of these values represents actinium itself cannot be readily made, it is predicted that the true level of actinium in the liver will probably rise to approximately 60 percent and that of the skeleton will fall to 20 percent. The validity of this prediction is based on the fact that the significant fractions of radio-thorium and AcX still present in the tissue samples from the injected material are not accumulated in the liver to any significant degree and show a high accumulation in the

1175115

bone, since these two radio-elements are isotopes of thorium and radium respectively. To summarize the situation, it appears both on the basis of the tracer studies and the radioautographic experiments that the actinium is deposited following intramuscular injection in a manner very much like americium, curium, and the lanthanide rare earths.

Cerium. The assays have been completed on a 256 day cerium experiment in which a group of 3 rats received this long-lived fission product in a carrier-free state by intramuscular injection. Unfortunately, the recovery value, i.e. the fraction of measured activity from all tissues and excreta, has been found to be 65 percent of the administered dose. The origin of the errors involved are not apparent. In view of this level of recovery, which we consider inadequate for the quantitative interpretation of the data, we will repeat this particular experiment. However, it is of interest to note that the concentration of cerium in the skeleton, liver, and most of the other organs and tissues at this time interval, on both the per organ and per gram wet weight basis, becomes essentially indistinguishable from the 256 day data observed for americium and curium if a correction factor for the cerium data of approximately 1.58 is applied to compensate for the low recovery. We believe that such a correction is probably reasonable in light of the fact that the most probable source of error was the determination of the cerium content of the excreta during the first month of these studies and it will be recalled that it was during this time interval that most of the cerium was excreted from the body, principally the liver.

Uranium 233. The 64 day intramuscular series with $U^{233}$ have been completed. The major points of interest are as follows: 9.11 percent of the administered uranium is found to be present in the skeleton at the end of this interval, this value being the average of the observed deposition in three rats. The only other tissue to show any significant degree of retention at this extended time interval was the kidney with 0.23 percent of the administered dose. The per gram concentration in the bone, wet weight, is apparently twice that in the kidney. These results are quite similar in many respects to those which have been observed by other workers with this substance, notably those under the direction of Doctor Tannenbaum in Chicago, and the Rochester group. It would appear that uranium is not held in the bone quite as tightly as other members of the actinide series, the lanthanide elements, zirconium, yttrium, and the two alkaline earth members, barium and strontium.

Radio-Zirconium. Complete tracer studies both intramuscular and stomach tube have been set up with carrier free radio-zirconium. These represent a repetition of experiments done several years ago which were felt to be unsatisfactory with respect to quantitative accuracy. It was felt of value to establish more clearly the precise level of accumulation of this radio-element in the different soft tissues and the skeleton at varying intervals after parenteral administration.

1175116

## Decontamination Studies

### Effect of Zirconium Citrate on the Distribution and Excretion of Hexavalent Plutonium.

Treatment with zirconium citrate has been shown to increase the urinary excretion of Pu, and reduce the amount deposited in the skeleton (J. Schubert, Science, 105, 389 (1947), and project literature). It appears to be one of the most promising decontamination procedure thus far proposed.

To study further the effect of zirconium on the distribution and excretion of plutonium an experiment was set up involving the injection of Pu (VI) in rats. A solution of zirconium citrate (22 mg. Zr/ml., pH 6.0) was injected intraperitoneally into five animals 24 hours previous to, simultaneously with, and at 24 and 72 hours following the injection of 28 micrograms of hexavalent plutonium into the triceps area of the animals right arms. The dose of zirconium citrate was 6.5 ml./kg. A second group of five animals was injected with 12.5 percent sodium citrate solution (5.2 ml./kg.) at the same time intervals. A third group consisted of eight untreated plutonized controls. All animals used were adult female rats weighing approximately 250 grams. The animals were maintained on stock diet, and were sacrificed on the eighth day. Urine and feces were collected separately at the end of the first, second and eighth days.

The results are shown in the accompanying table (Table VI). It will be noted that the sodium citrate had no apparent effect on the distribution or excretion of plutonium. However, the animals treated with zirconium citrate retained only half as much Pu in the carcass, this difference being accounted for by a moderate decrease in the absorption from the site of injection and a two-fold increase in urinary excretion. These results confirm the results obtained by J. Schubert. It will be noted, however, that the fecal excretion was lower in the Zr treated animals.

### Effect of Zirconium Citrate on the Distribution and Excretion of of Quadravalent Plutonium.

In these experiments the rats used were mature adult females weighing 200-250 grams. They were maintained on the regular stock colony diet throughout the experiment. The dose of plutonium (quadravalent) was 28 micrograms in 1/4 cc isotonic saline at pH 2. It was administered by injection into the muscles of the triceps area of the right arm, or by injection into the left external jugular vein. Treatment consisted of intraperitoneal injection of a solution of zirconium citrate at pH 6, which contained 25 mg. zirconium per cc. Urine and feces were collected separately and analyzed for plutonium, as was the liver, kidney, femur and carcass. The difference in the plutonium content of the right and left arms gave a measure of the

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TABLE VI

Effect of Zirconium Citrate and Sodium Citrate on Pu (VI)

| | | Controls(8) | Sodium Citrate(4) | Zirconium Citrate(5) |
|---|---|---|---|---|
| Unabsorbed in right arm | | 47.2±8.0 | 34.3±6.4 | 55.9±11.9 |
| Carcass | | 27.3±4.6 | 27.8±2.4 | 14.6±3.8 |
| Femur | | 1.6±0.5 | 1.8±0.2 | 0.6±0.1 |
| Liver | | 4.6±1.1 | 6.4±1.6 | 4.4±0.8 |
| Urine | 24 hrs | 3.3±1.1 | 2.4±0.2 | 6.4±4.2 |
| | 48 hrs | 0.3±0.2 | 1.0±0.4 | 2.9±0.7 |
| | 8 days | 0.6±0.2 | 0.8±0.1 | 1.2±0.2 |
| | Total | 4.2 | 4.2 | 10.5 |
| Feces | 24 hrs | 0.8±0.8 | 1.5±1.0 | 0.1±0.5 |
| | 48 hrs | 1.0±0.7 | 2.5±0.9 | 0.2±0.5 |
| | 8 days | 7.1±4.5 | 5.3±1.0 | 2.9±0.6 |
| | Total | 8.9 | 9.3 | 3.2 |
| Recovery | | 96.9±7.9 | 87.0±6.4 | 91.6±6.7 |

(Values given are expressed as per cent of the administered dose of Pu plus or minus the standard deviation)

1175118

plutonium remaining at the site of intramuscular injection. Treatment consisted of 20-40 mg. zirconium administered 14 hours prior to the injection of plutonium, and 0, 24, and 72 hours following the dose of plutonium. The rats were sacrificed after eight days. The results are shown in Table VII. The values given are expressed as percent of the total plutonium absorbed from the injection site.

TABLE VII

| | | Controls (5 rats) | Zirconium Treated 20 mg. Zr (5 rats) | Zirconium Treated 40 mg. Zr (4 rats) |
|---|---|---|---|---|
| Unabsorbed at injection site (% of dose of Pu) | | 77.1±9.6 | 87.9±7.9 | 82.4±5.7 |
| Percent of absorbed Pu | | | | |
| Urine | 0-24 hrs | 0.09-0.04 | 9.6±8.8 | 17.6±5.9 |
| | 24-60 hrs | 0.4 | 4.4±2.6 | 10.4±2.6 |
| | 60-192 hrs | 0.3±0.2 | 2.6±1.7 | 2.6±2.6 |
| | Total | 0.8 | 16.6 | 30.6 |
| Feces | 0-24 hrs | 1.8±0.9 | 2.6±2.6 | 4.6±4.6 |
| | 24-60 hrs | 0.9±0.2 | 1.7±0.8 | 1.3±0.3 |
| | 60-192 hrs | 4.5±0.4 | 4.1±1.7 | 3.3±0.7 |
| | Total | 7.2 | 8.4 | 9.2 |
| Femur | | 3.0±0.4 | 1.6±0.9 | 1.4±0.6 |
| Liver | | 9.7±1.4 | 10.5±3.5 | 11.8±2.0 |
| Carcass | | 76. ±37 | 62 ±40 | 48 ±14 |

These results show a tremendous increase in the urinary excretion of absorbed plutonium in the treated animals, as compared to the controls in which urinary excretion was almost negligible. There was little difference in fecal or liver Pu, but the amount deposited in the femur and retained in the carcass was less in the treated rats.

Experiments were also conducted in which the rats were injected with 25 mg. Zr (as citrate) at 2 1/2, 60 and 120 hours after the administration of Pu(IV) intravenously. The animals were sacrificed at the end of 7 days. The results are shown in Table VIII, and are expressed as percent of total plutonium recovered.

1175119

TABLE VIII

| | | Controls (5 rats) | Treated (4 rats) |
|---|---|---|---|
| Urine: | 1 1/2 days | 1.1±0.3 | 33.0±8.6 |
| | 7 days | 1.2±0.5 | 4.5±0.9 |
| | Total | 2.3 | 37.5 |
| Feces: | 1 1/2 days | 6.8±1.4 | 7.1±2.0 |
| | 7 days | 13.4±5.7 | 10.2±5.5 |
| | Total | 20.2 | 17.3 |
| Liver | | 15.5±418 | 18.3±5.2 |
| Kidney | | 2.1±0.8 | 0.7±0.1 |
| Femur | | 2.9±0.8 | 1.0±0.1 |
| Carcass | | 57.0±8.8 | 25.0±9.2 |

These results also show a great increase in the excretion of Pu(IV) in the urine in the treated animals, and a significant (threefold) decrease in the amount of plutonium deposited in the femur and retained in the carcass and kidneys. There does not appear to be any significant difference in the fecal or liver Pu. The relatively high value for the liver may indicate the presence of some colloidal Pu in the injected dose.

One may conclude that treatment with zirconium citrate greatly increased the excretion of Pu(IV) in the urine, whether the plutonium was administered intramuscularly or intravenously. There was also a significant decrease in the amount of Pu deposited in the skeleton and retained in the carcass. The effect on urinary excretion was greater with the larger dose of Zr, suggesting that it may be a "carrier" effect. No significant change in liver or fecal plutonium was observed as a result of treatment. In the animals injected with Pu intramuscularly, the amount absorbed from the injection site was so small that only a small part of the total administered dose was absorbed and subsequently excreted. However, in the intravenously injected animals, the increased urinary elimination amounted to over one third of the total dose. This confirms the results of the previous experiments with Pu(VI) and indicates that treatment may have a very real value in decontamination. This procedure should also be of value in studying certain fundamental problems in plutonium metabolism.

1175120

Effect of Zirconium Treatment on the Excretion and Body Distribution of Intramuscular Yttrium.

Treatment with zirconium citrate has been shown to increase the urinary excretion of both quadravalent and hexavalent plutonium. In the present experiment, the effect on the excretion of intramuscular yttrium was investigated to determine whether similar results might be obtained and to test the usefulness of the easily measured beta active yttrium in place of plutonium. The isotope used was $Y^{90}$ formed from $Sr^{90}$, and prepared free from the parent strontium. The dose was approximately 25 microcuries when injected and contained 1-2 micrograms of yttrium. The animals used were all mature female rats weighing around 250 grams. They were injected with radio-yttrium in the muscle of the triceps area of the right arm. Zirconium treatment consisted of 40 mg. zirconium as citrate injected intraperitoneally. All the treated rats received zirconium immediately after the dose of radio-yttrium with a subsequent dose of zirconium one day later. In addition, the second group received zirconium one day before the yttrium, while the third group were given zirconium 4,2, and 1 day prior to the yttrium. Five untreated rats served as controls. The animals were sacrificed on the third day following radio-yttrium administration and the tissues and excreta were analyzed for radioactive yttrium. The recovery was good in all cases. The results obtained, corrected to 100 percent, are shown in Table IX.

Urinary excretion of radio-yttrium was markedly increased in all the treated animals, indicating an effect similar to that obtained with plutonium. However, prior treatment with zirconium did not appear to enhance the excretion, suggesting that the effect is not due to saturation of bone groups with the metal. The fecal elimination was considerably reduced in the zirconized animals, but the over-all excretion was still much greater than in the controls. This was associated with a reduction in the amount of yttrium retained in the carcass and skeleton, although the effect here was not as great as has been obtained with plutonium.

In conclusion, zirconium treatment appears to have the same effect on radio-yttrium as on plutonium, the most striking feature being the great increase in urinary excretion. This experiment suggests that the effect is not due to saturation of bone groups with zirconium, but may be due to exchange with yttrium in bone, or to a "carrier" effect. Aside from its potential value in decontamination, zirconium treatment should be of great value in studying the fundamental metabolism of these metals in bone.

1175121

TABLE IX

THE EFFECT OF ZIRCONIUM CITRATE TREATMENT ON THE EXCRETION AND DISTRIBUTION OF RADIOACTIVE YTTRIUM ($Y^{90}$)*

| Each rat given 40 mg zr at each treatment | Experimental Groups | | | |
|---|---|---|---|---|
| | Control | I | II | III |
| Number of rats | 5 | 5 | 5 | 5 |
| Time Zr Administered Relative to $Y^{90}$ Injection | none | 0 Time<br>1 Day | -1 day<br>0 Time<br>1 day | - 4, - 2,<br>- 1 days<br>0 time<br>1 day |
| % Unabsorbed at Injection Site | 37.5 ± 2.1 | 32.2 ± 1.4 | 24.8 ± 2.8 | 30.1 ± 3.8 |
| % Carcass | 29.9 ± 10.1 | 16.9 ± 3.1 | 15.8 ± 1.8 | 21.8 ± 3.7 |
| % Femur | 0.7 ± 0.1 | 0.4 ± 0.1 | 0.5 ± 0.1 | 0.5 ± 0.1 |
| % Urine | 8.4 ± 1.4 | 41.0 ± 2.9 | 46.2 ± 2.4 | 26.8 ± 9.6 |
| % Feces | 19.8 ± 7.6 | 8.3 ± 0.9 | 11.9 ± 2.6 | 19.3 ± 8.6 |
| Total Excretion | 28.2 ± 8.6 | 49.3 ± 2.5 | 58.1 ± 3.2 | 46.1 ± 2.9 |

*Values given are expressed as percent of the dose of radio-yttrium recovered, plus or minus the standard deviation.

1175122

## Effect of Local Treatment on the Absorption of Plutonium (VI) from Intramuscular Injection and its Subsequent Distribution and Excretion.

Since a number of experimental conditions had been found to alter the absorption of intramuscularly injected plutonium, it was decided to investigate the effect of local treatment of the region of injection with cysteine, zirconium citrate or sodium citrate. Adult female rats were used for the experiments. The treatment consisted of intramuscular injection of 1 cc into the muscles on the posterior surface of the right arm. The animals were divided into three groups.

I. Controls: 1 cc isotonic (0.9%) sodium chloride.
II. Cysteine: 1 cc of a 0.25M solution of cysteine hydrochloride.
III. Zirconium citrate: 1 cc containing 24 mg Zr as citrate.

Fifteen minutes later, the animals were injected in the same area with 1/4 cc containing 14 micrograms Pu(VI) at pH 2. Urine and feces were collected separately and the rats were sacrificed after 4 days. The results are shown in Table X.

As was observed earlier, local treatment with cystein appears to reduce the absorption of plutonium from the injection site, possibly by reducing the hexavalent to the less soluble quadravalent state. Both sodium citrate and zirconium citrate increased the absorption from the injection site, the latter also causing a sharp increase in urinary excretion, while the former increased the fecal elimination of plutonium. The possible value of these procedures in treatment is still rather questionable and open to further investigation.

## Radio-Chemical Isolation

A method was developed for the separation of radio-calcium from a scandium target. This method consists of repeated precipitations of calcium flourido, carried by iron flourido with amonium flourido, the iron flourido separated by repeated extraction with ether. This procedure for the separation of radio-calcium is different from the method developed by the Clinton Laboratory but is not necessarily better.

Radio-cadmium was extracted from a silver target by a method reported in the literature for the separation of micro quantities of cadmium from macro quantities of silver. This consists of complexing the silver with amonium thiocyanate, then extracting this solution buffered to pH 5 with pyridine-chloroform solution. The last traces of silver are removed by further extraction with dithizone reagent.

1175123

TABLE X

EFFECT OF LOCAL TREATMENT ON THE ABSORPTION AND DISTRIBUTION OF PLUTONIUM (HEXAVALENT) ADMINISTERED BY INTRAMUSCULAR INJECTION

| Group | I. Controls | II. Cysteine | III. Citrate | IV. Zr Citrate |
|---|---|---|---|---|
| No. of rats | 5 | 4 | 4 | 5 |
| Unabsorbed Pu at Inj. Site | 39.1 ± .32 | 55.1 ± 6.1 | 18.2 ± 13.6 | 18.1 ± 7.1 |
| Excreted in Urine | 4.3 ± 0.7 | 2.9 ± 3.0 | 4.5 ± 1.2 | 14.6 ± 7.2 |
| Feces | 4.8 ± 2.2 | 2.4 ± 0.7 | 12.5 ± 7.4 | 5.6 ± 1.8 |
| Deposited in Femur | 1.5 ± 0.3 | 0.9 ± 0.1 | 1.9 ± 0.5 | 0.6 ± 0.1 |
| Liver | 4.3 ± 0.6 | 2.7 ± 1.0 | 5.3 ± 1.7 | 4.8 ± 1.8 |
| Carcass | 24.8 ± 5.1 | 14.9 ± 2.7 | 33.7 ± 10.2 | 14.2 ± 1.6 |

Values given are percent of dose of Pu ± Standard deviation.

1175124

The cadmium is removed from the silver at a pH of 3, the dithizone having been disolved in chloroform.

A molydenum target was bombarded with approximately 105 microamperes of deuterons and allowed to decay for 4 days before milling off the top active component. Approximately 1.7 grams of the metal milled from the target was disolved in aqua regia and evaporated almost to dryness. The residue was disolved in 5 ml of $H_3PO_4$ and 15 ml $HClO_4$ added. After the mixture was heated in an oil bath to 200-210 degrees, technetium was distilled by dropping 20 ml hydrobromic acid into the mixture with a stream of carbon dioxide. In this manner approximately 275,000 counts per second of technetium was obtained, identified as the 110 hour half-life isotope.

A sample of radio-zirconium and radio-columbium was received from Oak Ridge. This was assayed and an aliquot containing approximately 4 millicuries was utilized for separation of the two components. Separation was accomplished by use of selective absorption of columbium on $MnO_2$ in 10 N $HNO_3$, the $MnO_2$ being formed by oxidation of manganous ions by potassium chlorate. It was determined that the same high percentage of separation was obtained by addition of manganese dioxide to the 10 N $HNO_3$ solution and heating in a water bath for 20 minutes. Two separations of this type were made. The amount of activity found in the zirconium fraction amounted to approximately 50 percent of the total activity.

Plans are being made to use ion change columns for the isolation of radioactive rare earths in the carrier-free state. This procedure is to be employed for the preparation of carrier-free rare earths extending from gadolinium to lutecium following cyclotron bombardment. The purpose of preparing and utilizing radioactive carrier-free rare earths is to observe if the gradual change in the chemical properties of successive members of the series is reflected in the metabolic pattern of such substances. It is of particular interest to see whether the high liver accumulation and radioautographic pattern noted with lanthanide group of rare earths continues with the second half of the rare earth series.

A short bombardment of about 10 microampere hours was made on a ruthenium target for the purpose of studying yields of radioactive elements obtained. Preliminary studies indicate yields in decreasing amounts of radio-rhodium, technetium, and radio-molybdenum. The yield of molybdenum is very small.

1175125

## II. BIOLOGICAL STUDIES OF RADIATION EFFECTS

J. H. Lawrence - in charge

Project 48A

### Lethal Effects on Mice of Fast Neutrons from the 184-inch Cyclotron

R. Lowry Dobson

Preliminary experiments designed to test the biological effectivness of 90 Mev neutrons available from the 184-inch cyclotron beam have been carried out, using mice as test objects and lethal action as the phenomenon looked for. Bagg albino mice during exposure were confined in ventilated compartments in a wooden cage, surrounded on all sides but the bottom with a three-inch thickness of paraffin slabs. The cage was placed directly in the beam inside the concrete shielding of the cyclotron and approximately fifteen feet from the source.

Since primary interest was given to tissue doses which would be delivered to internal regions of the body of a larger animal if exposed directly to the beam, the paraffin slabs were placed in front of the mice in the path of the oncoming beam and around the cage in order to assure an equilibrium density of secondary protons inside the exposure chamber. Ionization measurements were made with a 25 r and a 100 r Victoreen thimble chamber inside the cage. [1] Hence the ionization measured, and the ionization to which the animals were subjected, was due almost entirely to the secondary protons produced in the paraffin. Loevinger[2] has recently studied the problem of measuring the tissue dose of 90 Mev neutrons; our experimental set-up and dosage calculations have made use of his data.

Mice were exposed to various doses given at various dose rates. In one experiment five groups of six animals each were exposed, at a rate of 1,065 rep/hr, to doses varying from 445 rep to 815 rep. 100 percent mortality in 45 days was found in the group receiving 815 rep; the LD 50/45 days was found in two groups receiving 625 rep and 715 rep respectively. None of the animals in the lower dose ranges died. If the LD 50/45d for this experiment is taken to be 670 rep, the corresponding neutron dose measured in "n" at the outer surface of the paraffin was 238.

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1) There is some question as to whether or not the collecting voltage in Victoreen chambers is large enough to give saturation currents under the conditions which obtained during these bombardments. This point is being tested further.

2) Loevinger, R. BP-139, October 21, 1947.

1175126

In another experiment, when two groups of 12 animals each were exposed to 715 and 880 rep respectively given at a rate of 318 rep/hr, the LD 50/45d was found to lie somewhere between the two doses; 25 percent and 92 percent mortality were found in the repective groups.

At the still lower dose rate of 164 rep/hr, given to six groups of 25 animals each and amounting to doses varying from 660 rep to 1,320 rep, no significant differences in mortality which could be attributed to the radiation were found among the various groups. The mortality in the group receiving 1,320 rep was only 12 percent in 100 days; the mortality in the group receiving 660 rep was 16 percent. Thus at this low dose rate the animals withstood 1,320 rep given (taking into account the five rest periods of about 10 minutes each for the removal of the animals receiving lower doses) in about nine hours. This dose would correspond to 470 n if the beam had been measured outside of the paraffin.

Although the numbers of animals were not large, these preliminary experiments seem to indicate a large time-dose relation factor in the lethal action of high energy neutrons and their secondary protons.

This work needs repetition and check, and is being continued with further studies on dosage measurement and effects of these radiations on animals.

We are indebted to Dr. B. Moyer and his group for their help and advice in these studies.

## Lethal Effects on Mice of 180 Mev Deuterons from the 184- inch Cyclotron

C. A. Tobias, Patricia Weymouth, R. Lowry Dobson and Hal Anger

The first biological experiment with the direct beam of the 184 inch cyclotron was an attempt to determine lethal effect of 180 Mev deuterons on mice. The experiment was designed to demonstrate the time of death with a wide range of dosage. Swiss mice were divided into 5 groups of 50 mice each. The groups received the following approximate doses: I, 100 rep; II, 330 rep; III, 1,000 rep; IV, 3,000 rep; control, 0. Each of these doses was delivered in less than 1 minute. The control mice were transported to the cyclotron site and kept with the experimentals throughout the run and were, therefore, exposed to the same temperature change and background irradiation as the experimental animals.

Within 10 days after bombardment, all animals in groups III and IV died. Variation in lethal effect between the two groups was not significant, although there was a tendency for a slightly slower death

1175127

rate in group III. No animals have yet died in the other groups (30 days since exposure).

The average weights showed a marked drop of over 5 gms. for groups III and IV in the first 3 days after treatment. In Group II the weight loss at 3 days was about 2 gms. and in Group I, 0.5 gms. The animals of Group I regained their orignial weight in the period of one week, while those of Group II after 2 weeks time were still 2 gms. below their orignial weight.

The white blood cell count of all groups showed a very marked drop in the first 24 hours; returned to normal in 3 days in Group I and remained depressed for at least 10 days in Group II. The red blood cell count was not affected in any group. The work is being continued.

We are indebted to Dr. B. Moyer and his group for their help and advice in the course of this work.

## Rate of Metabolism of $CO_2$

Harden Jones, M. Calvin
C. Heidelberger, Glenn Sheline

The rates of metabolism to $CO_2$ of administered radiocarbon-labeled acetate, glycine, glucose, and tyrosine have been studied. Following intravenous administration each substance has its characteristic rate of oxidation. The $CO_2$ production is in two rate determined parts a "rapid rate" phase and a "slow rate" phase. It is believed that the rapid phase coincides with oxidation of the substance administered while the slow phase is oxidation of other substances which have been derived from the labeled compound administered. The time constants of oxidation are indicative of the rate of utilization of the pool of stubstances which are in metabolic equilibrium with the labeled substance. The following time constants are listed for "A" - strain mice:

| | $K_1$ (minutes) | $K_2$ (minutes) |
|---|---|---|
| ACETATE | | |
| NORMAL | 0.062 ± .008 | 0.0046 ± .002 |
| TUMOR MICE | 0.070 ± .008 | 0.0051 ± .0013 |
| GLYCINE | | |
| NORMAL | 0.048 ± .008 | 0.0018 ± .0008 |
| TUMOR MICE | 0.040 ± .006 | 0.0028 ± .005 |
| GLUCOSE | | |
| 1-NORMAL | 0.028 | ----- ? |
| 1-TUMOR MOUSE | 0.034 | 0.0054 |
| TYROSINE | | |
| 3 TUMOR MICE (POOLED) | 0.0073 | 0.00014 |

1175128

The rates of oxidation appear to be characteristic for each of the above substances and there are not obvious or significant differences in the metabolism of these substances in normal and neoplastic animals.

## Further Experiments Concerning the Biological Effects Due to Uranium Fission

P. Weymouth and C. Tobias*

### Part A
### Alpha Particle Radioautography

In previous progress reports (see Monthly Progress Reports for March and April of 1947) it was demonstrated that $UO_2$ colloids of .15 micron average particle diameter are mostly taken up in the liver and spleen with a small fraction of the colloid, 2-5 percent, being found in the bone marrow. The distribution of the colloid was further studied by means of radioautography. One mouse was sacrificed 24 hours after I.V. injection of 2 mg. of the $UO_2$ colloid suspended in .33 cc of 5 percent glucose. Ten micron undecalcified sections of femur in celloidin were prepared for us by Dorothy Axelrod. These sections were placed on Eastman alpha particle plates under water and the plates exposed for one month period.

Although the staining technique has not yet been properly developed, the section showed that most of the uranium was deposited in the marrow, in the shaft of the bone, and in the epiphysis in the zones of ossification. In these areas, the uranium deposition was heavy enough to give star formation. In addition, single alpha tracks appeared in the emulsion throughout the area which had been in contact with the bony matrix, indicating a uniform distribution, but low concentration of uranium in the bone itself. One or two stars and a few single tracks were noticed originating from the periostoum. The work is being continued with a view to further identify the microscopical distribution of $UO_2$ in bone marrow.

### Part B

### Comparative Effectiveness of Beta Rays, Alpha Rays, and Fission Recoils

We previously reported (Monthly Progress Report for April, 1947) that the lethal effect of phosphorus beta rays from the phosphate colloids required about 27 times the dose required for lethal effect from fission recoils of $U^{235}$ from $UO_2$ colloids. The basis of the comparison was not too good because the uranium colloids had a slightly different distribution from the chromic phosphate colloids. Relatively

* With the technical assistance of J. Luce and C. Tregillis

1175129

more $UO_2$ was taken up in the bone marrow. The beta ray part of the experiment has now been repeated with $UX_1$ and $UX_2$ in the form of $ThO_2$ colloid obtained from Oak Ridge as a by-product of the magnetic separation process of uranium. The same particle size colloid was used as in the case of the $UO_2$, and the distribution in the body was found to be nearly the same. Table XI shows typical distribution of both $UO_2$ and $ThO_2$ in mice one and ten days after injection. Fifty-four mice received 150 microcuries each of $UX_1$ and $UX_2$. All of these animals died, the mean period being 14 days. They were observed continuously.

Post mortem findings were as follows:*

> Spleen, uniformly small and dark; lung, often congested and hemorrhagic; liver, occasionally pale; other tissues normal; sero-sanguinous fluid in thoracic and peritoneal cavities in 4 cases. Histological sections showed: testes, pancreas, lymph nodes, and adrenals essentially negative; kidney, variable degrees of congestion particularly of the glomeruli and granular swelling of the cells lining the tubules; lung, variable degrees of congestions, hemorrhage, edema and acute inflammation usually confined to the interstitial tissue; spleen, atrophy, fibrosis, depletion of lymphocytes and deposition of material within the macrophages which seemed to be increased in number; liver, necrotic changes including loss of cytoplasmic detail, pyknosis, and karyorrhexis usually confined to the mid-zonal region but occasionally occupying almost the entire lobule, and in some instances, diffuse infiltration with polymorphonuclear cells. Blood cultures from 18 mice yielded rather unsatisfactory results, but only two were sterile. Of the 16 which showed growth all but 2 contained organisms suggestive of bacterial invasion of the blood which may take place as early as 2 - 4 hours before death. The two cultures which were indicative contained Salmonella typhi-murium and Streptococcus pneumoniae. We are indebted to Dr. A. P. Krueger who examined the cultures. The mice lost weight continuously (see Fig. 1), the average weight loss at 10 days being 6.5 gms. Terminal blood counts, taken 1/4 to 4 hours prior to death, on 19 mice showed marked leukopenia and anemia; the average white blood cell count was 2,600/cmm, average red blood cell count $3.83 \times 10^6$/cmm (see table XII).

These extensive data serve to show that the mice probably died of radiation effects with the possibility of secondary infection such as mouse typhoid or pneumonia particularly where the blood culture showed these organisms. The symptoms prior to death, the post-mortem picture of decreased spleen size, hemorrhage, the liver and spleen histological changes (histological changes in the kidney may be partially the result of a small dose of soluble heavy metal, but the

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* We are indebted to Dr. Paul Roschn for helping with the microscopic examinations.

TABLE XI

TYPICAL DISTRIBUTION OF U AND Th AFTER I.V. INJECTION OF COLLOIDAL $UO_2$ AND $ThO_2$

(Average particle diameter approx. 0.15$\mu$)

| Material | $UO_2$ | | $ThO_2$ | |
|---|---|---|---|---|
| Days after Inj. | 1 day | 10 days | 1 day | 10 days |
| Tissue | % Injected Amount[1] | | | |
| Liver[2] | 68.0 | 77.0 | 86.0 | 83.0 |
| Spleen[2] | 22.3 | 14.0 | 3.0 | 5.0 |
| Kidney | .6 | 0.5 | 0.2 | 0.1 |
| Lung | 1.0 | 0.9 | 0.5 | 0.6 |
| Gut | 1.0 | 1.0 | 1.0 | .9 |
| Carcass[3] | 6.7 | 5.3 | 9.2 | 9.9 |
| Urine[4] | 0.06 | 0.3 | 0.02 | .06 |
| Feces[4] | 0.34 | 1.1 | 0.08 | .44 |

1. The observed values were slightly adjusted proportionally to add up to 100%.

2. Liver and spleen values differ in individual determinations from the average given here by about 7% r.m.s. of the initial dose.

3. Including muscle, skin, skeleton.

4. Total excreted in 1 and 10 days.

1175137

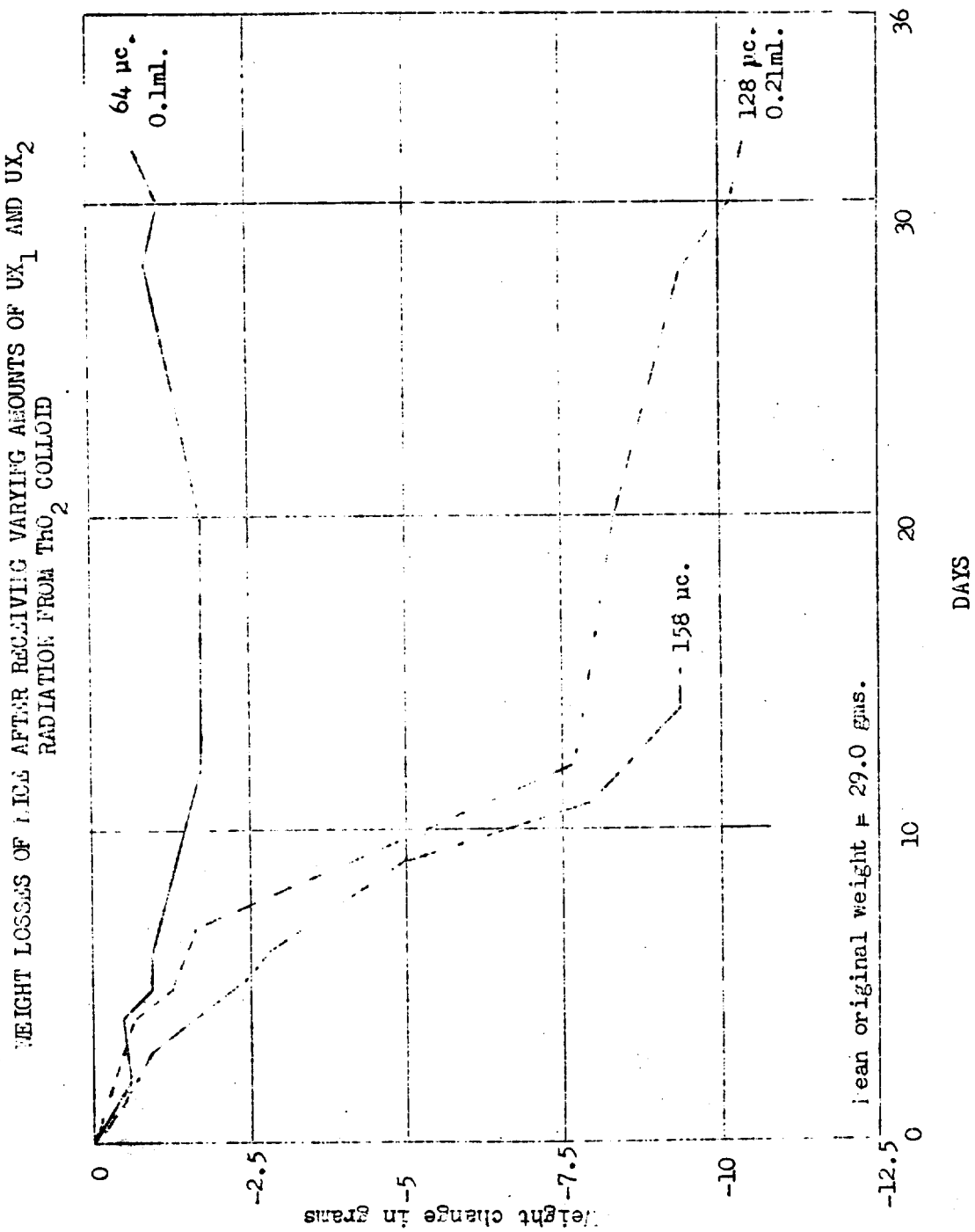


Figure 1

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TABLE XII

TERMINAL BLOOD COUNTS OF MICE AFTER INJECTION OF $UX_1$

| Mouse No. | WBC x $10^{-3}$ | RBC x $10^{-6}$ | Platelets x $10^{-3}$ | Wt. gms. | Approx. time before death, hr. |
|---|---|---|---|---|---|
| 8 | 4.60 | 1.29 | 110 | 14.5 | 1 1/2 |
| 9 | 10.45 | 12.38 | 240 | 18.0 | 0 |
| 11 | 1.35 | 2.64 | 110 | 15.1 | 2 1/2 |
| 12 | 1.05 | 2.07 | 110 | - | 2/3 |
| 15 | 1.00 | 3.63 | 210 | - | 1 1/4 |
| 18 | 2.75 | 2.28 | 60 | 19.1 | 1/2 |
| 19 | 2.35 | 2.94 | 250 | 20.2 | 0 |
| 20 | 2.60 | 3.28 | 270 | 17.6 | 0 |
| 22 | 1.20 | 4.05 | 220 | 18.7 | 3/4 |
| 23 | 1.75 | 6.68 | 390 | 19.8 | 0 |
| 27 | 5.35 | 3.72 | 350 | 17.2 | 0 |
| 28 | 2.05 | 2.87 | 130 | 18.9 | 1/2 |
| 29 | 1.05 | 2.05 | 120 | - | 0 |
| 30 | 2.40 | 5.18 | 220 | 14.9 | 0 |
| 33 | 1.40 | 3.55 | 350 | - | ca 8 |
| 34 | 0.75 | 5.64 | 650 | 16.2 | 1/4 |
| 35 | 1.90 | 3.81 | 310 | 17.5 | 1 |
| 36 | 3.15 | 3.07 | 410 | - | ca 2 |
| 37 | 2.20 | 1.69 | 90 | - | - |
| AVERAGE | 2.60 | 3.83 | 242 | 17.5 | |
| Normal avg. | 23.7 | 9.95 | | 25.0 | |

117513

damage was insufficient to contribute to lethal effect) and the leucopenia and anemia all point to acute radiation effects.

In addition a second preparation of $UX_1$, as colloidal $ThO_2$ (0.1 mg) was injected intravenously in a volume of 0.2 ml. or less into two further groups of mice. The first group, consisting of 10 mice, received 128 uc, and 6 died in 7 weeks. The second group, 25 mice, received 64 µc and only one died in 7 weeks, the length of the experiment to date.

It appears that the lethal effects that occured in the first group of mice that received 158 microcuries of $UX_1$ were quite similar in time of appearance to those that occured after irradiating mice which contained 2 mg. enriched uranium with slow neutron beams. The second group that received 128 microcuries died in a rather similar fashion to one of the uranium control groups in the experiment cited above. The figures thus obtained make a new comparison possible between the effectiveness of alpha rays, beta rays and fission recoils. It is still quite apparent that fission recoils are more effective in producing lethal effects than alpha and beta rays. The numerical results are listed in Table XIII. It appears that lethal effect on Bagg albino mice may be achieved by beta rays only if about 22 times the energy equivalent dose is given to the liver (previously we cited 27). The same factor for comparing alpha particles and beta particles appears to be about 10, in good agreement with other determinations.

1175134

TABLE XIII

COMPARATIVE DOSES RECEIVED BY MOUSE LIVERS IN LETHAL EXPERIMENTS WITH BETA, ALPHA, RADIATION AND FISSION

| Mode of Irradiation | Rapid lethal effects. Mean time of death approx. 14 days. | Slow lethal effects. Mean time of death approx. 35 days. |
|---|---|---|
| Enriched Uranium$^{235}$ + neutrons. Approx. 85% of radiation within a few hours | 3,700 rep | |
| $P^{32}$ Irradiate continuously Beta rays | ~100,000 rep | ~100,000 rep |
| $UX_1 + UX_2$ Irradiate continuously Beta rays | ~ 60,000 rep | ~95,000 rep |
| Enriched uranium alpha particles | - | ~ 9,800 rep* |

* 130 rep in bone marrow

1175135

# III. BIOLOGICAL EFFECTS OF RADIATIONS FROM EXTERNAL AND INTERNAL SOURCES

R. S. Stone - in charge

Project NDP-48C
UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

## Administration

This project, started on OSRD subcontract to the University of Chicago, has continued to the present and is now part of the University of California program for the Atomic Energy Commission. Early reports were published in the CH reports from the University of Chicago. No scientific report has previously been made through the Radiation Laboratory and hence the present progress report is somewhat general in nature, the attempt being to bring the readers up to date on what has taken place in the past. Future progress reports will be somewhat more specific and detailed.

Doctor Low-Beer has been continously in charge of the program involving the hematological effects. He was assisted by Miss Jing as laboratory technician up to October 1947. Miss Jing has been replaced by Miss Anna Poulsen who has been with Doctor Low-Beer since September 1947. Many other doctors and technicians aided in this work insofar as the clinical side of the patients care is concerned. The particular hematological problems have been discussed with different hematologists, but especially with Doctor Paul Aggeler.

Doctor Miller started the second section for the study of radio-iodine in 1946, because of the previous work with iodine at the University of California Medical School by Doctors Soley, Hamilton and others, and the knowledge gained previously on radiation effects by Doctors Stone, Low-Beer, etc. Doctor Miller has had the technical assistance, successively, of Miss Siiri Markkanen and Mr. Harrold Brook Knowles, Jr. since November 1946. He has had the professional assistance of Doctor Nadine Foreman. We have enjoyed the cooperation of the technical and scientific staff of other parts of the Radiation Laboratory; they have part-time secretary to the Project was Mrs. Alice Bennett, then, for a time, the secretary of the X-ray Department, Miss Elena Bogdanoff took on the responsibilities of secretary to 48-C.

1175136

## Hematological Effects of Total Body Irradiation

## From External and Internal Sources

B.V.A. Low-Beer

The objective of this project has been to investigate the effect of therapeutic doses of ionizing radiations on the blood elements of human subjects. Patients selected for this study were those whose disease required therapeutic irradiation of the entire body. The patients were selected for treatment with radiations and so treated by physicians on the staff of the University of California Medical School. Advantage was taken of the fact that they were being so treated to observe the effects on their blood picture. The clinical condition was followed by their physicians in the usual course of events and is not reported here. X-rays produced by electrical potentials of 100 kv, 200 kv and 1000 kv were used for external radiation and radioactive phosphorus was used as a source of internal irradiation. From the inception of the project in October 1942 to June 1946 twenty-nine patients treated with external x-ray irradiation were studied. Two patients were treated with daily doses of 5 r; 5 patients with 10 r doses; 17 patients with 20 r doses; 2 patients with 15 r doses; 1 patient with 30 r and 1 patient with 50 r daily doses. All measurements were made on the skin. The treatment course varied from 5 to 92 days. The total body exposures varied between 100 r and 390 r (skin), 300 r being the most frequent total. The calculated dose in the center of the body varied from approximately 60 r to approximately 200 r (tissue).

Studies included determinations of hemoglobin, red blood cell count, white blood cell count, platelet count, differential count, lobation index of polymorphonuclear neutrophiles, sternal marrow studies, prothrombin time, sedimentation rate, hematocrit and icterus index. The observation period extended from one to three years following treatment.

The most consistent change noted was an absolute and relative decrease in the number of lymphocytes following treatment, irrespective of size of the dose and of physical factors of treatment. Such decreases were followed by recovery during the post-treatment period. Marked fluctuation in total white blood cells and neutrophile counts were observed frequently during the treatment period, but these could not be correlated with the size of the dose and physical factors of treatment. In the post-treatment period fluctuations occured in the number of polymorphonuclear cells of a significant number of patients who had been treated with 1000 kv generated x-rays, around 60 days after conclusion of treatment. A left shift of the polymorphonuclear neutrophiles was observed in the nine patients in whom this factor was followed. This shift occurred without relation to the total polymorphonuclear cell count. Monocytes showed marked lability which was related to the size of the individual dose. Patients who received individual doses greater than 10 r showed increased monocyte counts as a general pattern of fluctuation during treatment and in the early post-treatment period. In the later post-treatment period the monocyte

1175137

count returned to pre-irradiation values.

The erythrocyte count and hemoglobin occasionally showed a significant decrease during the course of treatment. This was followed by recovery to pre-irradiation levels in the early post-treatment period. Characteristically, in the late post-treatment period, around 250 days after conclusion of treatment, there occured a temporary decrease in erythrocyte count, accompanied by a rise in hemoglobin. The picture at this time was one of macrocytic hyperchromic anemia.

Platelet counts, sternal marrow studies (nine patients), prothrombin time (nine patients), sedimentation rate, hematrocrit and icterus index showed no significant changes which could be attributed to x-ray effect.

From July 1946 to December 31, 1947, 31 patients were studied. Nine of these patients belonged to the group treated in the period October 1942 to June 1946. Three patients were treated with 100 kv x-rays, and 19 patients were treated with radioactive phosphorus given intravenously. Of the patients treated with x-rays, one received daily doses of 20 r (skin); the two others received daily doses of 10 r (skin). All received total doses of 300 r(skin). The total doses of $P^{32}$ varied from 3.5 to 8 millicuries given in weekly fractions. The highest single dose given was 2 millicuries.

Of the nine patients who had been treated in the period from 1942 to 1946, 4 showed markedly higher hemoglobin levels (approximately plus 30 percent) during this late post-exposure period as compared with pre-irradiation levels. Five of these patients showed markedly decreased platelet levels as compared with pre-irradiation values. No other significant changes were observed in any of the nine patients. It should be noted that all blood counts during the entire period of observation of these nine patients were made by the same technician and with no change in method or technique.

No significant hematological changes have been noted in any of the three patients treated with x-rays during the observation period, except for a very transitory decrease of lymphocytes shortly after conclusion of treatment. This occured in two of the patients.

Fourteen of the 19 patients treated with $P^{32}$ have been followed for a long enough time to permit comments on the effects of the radiations or the hematological condition. The most consistent effects shown by the fourteen patients are a temporary depression of the platelet count, a temporary decrease in prothrombin time, and temporary elevation of sedimentation rate. Fluctuations in erythrocyte count and hemoglobin values, and in total white blood count and the elements comprising the differential count, remained within physiological limits during treatment and post-treatment periods. Cutaneous hemorrhages, or tendency to bleeding were not observed in any of the patients.

Seven of the fourteen patients received gold therapy prior to treatment with $P^{32}$, and following $P^{32}$ treatment. The

1175138

temporary depression of the platelet count occured in all of the patients, however, so that it cannot be attributed to gold therapy.

In August 1947 the hematological project was enlarged further to include patients treated with radio-iodine. So far, 10 additional patients treated with radio-iodine are being studied. The observation period for patients added to the study from that time on is too brief to permit any evaluation at this time.

From July 1946 to December 1947, 553 hematological examinations were made in the study. All examinations included complete blood count with erythrocyte measurement and lobation index. In addition, approximately 100 prothrombin, cholesterol, hematocrit, and sedimentation determinations were made. Approximately 185 medical examinations were done on the patients.

Besides these laboratory studies, newly acquired items of equipment have been calibrated and standardized. Charts and graphs were made on all patients included in the study.

## Metabolism & Effects of Radio-Iodine ($I^{131}$)

Earl R. Miller

The purpose of the study of $I^{131}$ in patients has been primarily to determine harmful effects of $I^{131}$, acutely and over a long period of time in humans. In order to know the amount of exposure of the patient to the radiation from the radio-iodine, it is important to study means of determining uptake of the $I^{131}$ in the thyroid with the thyroid intact in the patient, and to study excretion of $I^{131}$.

Urinary excretion of $I^{131}$ from patients has been measured in most cases in which thyroid uptake studies were made in order to determine what portion of the iodine could be accounted for by thyroid uptake and urinary excretion by our methods, what errors there were in the methods, and what fraction of the administered $I^{131}$ was lost by other routes of excretion or was stored in other sites in the body.

Choice of Subjects. A few young doctors on the house staff of the University of California Hospital, fully cognizant of the dangers, volunteered to serve as normal controls. A series of patients were studied whose thyroid function was normal, but who were to have operations on the gland for nodules. This permitted study of the normally functioning gland as well as of the abnormal nodules. A number of patients were chosen for study whose primary disease was hyperthyroidism. The administration of relatively large doses of $I^{131}$ to these patients, was warranted as a treatment of their disease. This was a particularly valuable group because of the interest of the patient in himself and his disease and because of the interest of

the clinician in close laboratory and clinical follow-up. The last group of subjects were those in which carcinoma of the thyroid was suspected or proved. It was in this group that the largest number of tissue studies were made. In this group also, the administration of very large doses of $I^{131}$ was warranted.

Preliminary Clinical Work-up and Follow-up. In the normals, no special preparation was made. Thyroid uptake and urinary excretion was determined.

In subjects with nodules in the thyroid or with hyperactivity of the thyroid, histories were taken and physical examinations were done. The following laboratory determinations were made: blood count, urine examinations, blood cholesterol, basal metabolic rate, and protein bound iodine in the serum. In the subjects with hyperthyroidism, monthly follow-up examinations were made. These examinations essentially duplicated the preliminary work-up.

In those who went to operation, an attempt was made to measure the amount of $I^{131}$ in the removed specimen for comparison with the measurement of the thyroid uptake before removal. Autoradiographs were made of the removed tissue.

In the subjects with cancer, routine histories, physical examinations and laboratory studies were made. After the operation was performed, the normal and cancerous tissue was studied for uptake of $I^{131}$ by Geiger counter and autoradiographs. Where possible, preliminary in-situ measurements of $I^{131}$ uptake in the thyroid and urinary excretion measurements were carried out.

Doses of $I^{131}$ Administered. In the normals and in patients who were to be operated upon for nodules, a dose of 250 μc $I^{131}$ was given usually.

In subjects with hyperthyroidism, from 250 μc to 4000 μc was given in single doses. In some subjects, the doses were repeated so that totals of over 12,000 μc have been given over a period of a few months.

In subjects with cancer, a test dose of 2000 μc was given usually. In one person doses of 2000 μ , 7000 μc and 50,000 μc were given.

Technique of Administration and Measurements. The iodine was administered orally in the morning. The dose was carefully measured in c.c. by a remote controlled burette calibrated in .02 c.c. per division. The bottle containing the dose to be given was checked by Geiger counter for its $I^{131}$ content. Measurements of thyroid uptake were made at about noon and 4 PM of the same day, morning, noon and late afternoon of the following day, and in the morning of the third day. Where possible, another measurement one week later was made. In the 48 hours during which the initial thyroid measurements were made, all urine was collected, in some cases, in individual specimens, and in most of the cases in four 12 hour samples. The iodine content was determined in these.

If the patient was to be operated upon, a measurement of $I^{131}$ content of the thyroid was made just prior to surgery. The tissue removed at operation was taken from the operating room, measured on the counter and weighed. Microscopic sections were obtained. Autordiographs of these were obtained.

To determine the uptake of $I^{131}$ in the thyroid, it was first necessary to make a set of standards to be used as substitute or "dummy" thyroids. These consist of 30 c.c. rubber capped serum bottles. Each was filled with an aqueous solution of $I^{131}$ of known concentration, ranging from 10 μc to 5000 uc. These bottles were chosen because the solution in each was about the same weight as a moderately enlarged thyroid and it has approximately the same cross-sectional area and depth. These were placed on a wooden phantom resembling the neck in size, 53 cm below the face of a Geiger counter and the number of counts per minute from each was recorded. This is then graphed as counts per minute against uc $I^{131}$. A radium standard was used as a constant source of gamma rays for checking the constancy of the counter. The bell-shaped Scott mica window counter was mounted in a lead cylinder which has lead walls one inch thick and an inside diameter of 2 1/4 inches. The counter window was 7 cm from the mouth of the cylinder which pointed at the patient or specimen. The mouth of the lead cylinder was covered with a lead filter 1/8 inch thick. In this way, the counter "saw" a circle about 14 inches in diameter. Recently we have changed to a cylindrical Geiger counter.

The long distance between the thyroid and counter was chosen in order that the uncertainty due to the unknown depth of the thyroid in the neck would be reduced to a minimum. The heavy filtration in front of the counter was chosen so that the 80kv x-ray from $I^{131}$ would be completely absorbed. If this were not absorbed, it would introduce an error again because of the unknown depth and size of the thyroid. A shallowly located thin thyroid would absorb less of this component than would a thick, deeply located gland. In addition, since the amounts of iodine to be measured are large, the number of counts per minute were reduced sufficiently so that coincidence corrections were not troublesome.

In making the measurements of the $I^{131}$ content in the urine, the above considerations of distance and filtration do not apply since the urine specimen and the standard are put into identical containers. In these cases, since the amount of iodine in the samples is small, a short distance and thin filter were used.

Because of uncertainties in the counters and electronic equipment, a standard whose count is nearly that of the thyroid is measured each time a thyroid uptake determination was made.

When the uptake in a thyroid was to be measured, the subject was placed supine on a table and the Geiger counter, mounted on an x-ray tube stand, was moved over the thyroid. The number of counts per minute was recorded in this position. The counter was

then moved over the thigh and the counting rate in this position was determined. The thigh above the knee is approximately the size and shape of the neck and contains bone, muscle and blood as does the neck. The counting rate over this area should be the same as the counting rate over the neck if the thyroid were not present. The number of counts per minute due to the thyroid is accepted as the difference between those from the neck and those from the thigh.

Results of Measurements. In general, the thyroid takes up the circulating iodine very rapidly. The amount of iodine in the thyroid reaches a maximum in less than 24 hours, and in some cases within a very few hours. In general, the thyroid retains most of the iodine it selects from the blood stream. There is some evidence to suggest that the rate of uptake of $I^{131}$ in the thyroid is a function of thyroid activity. Because making those measurements is so time consuming, we at first concentrated effort on the late measurements. It was felt that the level of uptake could best be determined in this way. It becomes apparent now, that more effort is needed in studying the early part of the uptake curve.

The thyroids of the normal subjects took up from 5 percent to 35 percent of the administered $I^{131}$. The percent uptake of $I^{131}$ in any patient was apparently nearly independant of the size of the dose if the patient was in the same condition when the small and large doses are given, e.g. first tracer then larger dose. In general, the percent uptake of iodine in the thyroid is a fairly direct funtion of the thyroid activity. Subjects with thyroiditis and hypothyroidism have extremely low uptakes and subjects with hyperthyroidism have high uptakes. However, in spite of this generalization, no single test such as estimated thyroid size, B.M.R., protein-bound iodine in the blood, blood cholesterol or any combination of these allows us to predict with certainty what the uptake in a given patient will be. Previous iodine or drug (thiouracil or propythiouracil) therapy, and iodine in food may affect the amount of $I^{131}$ that the thyroid will accept and hold. Two subjects may be indistinguishable clinically and by laboratory tests, yet their iodine uptakes will be greatly different. It appears that this may be so because the one patient may be on his way to an exacerbation of hyperthyroidism (high uptake) and the other may be on his way to a remission from hyperthyroidism (low uptake). This has become an important by-product of the study that is useful clinically.

In certain cases it is possible to account for all of the administered iodine by adding urinary excretion to thyroid uptake but most of the time there is a definite and significant amount not accounted for when this is done. Some of this discrepancy may be because of faulty measurements but further study is needed to check these findings and further research is needed on animals and humans to study other routes of excretion and other storage depots in the body.

Results on Patients. In the patients with presumably normal thyroids,

1175142

with and without nodules, and those with hyperactive thyroids, to whom small doses (250 μc) were given, no effects were recognized. In patients with cancer of the thyroid to whom amounts up to 200 μc $I^{131}$ were given, there were no noticeable effects, but many more observations are needed and further follow-up is essential. The last report on one patient with widespread functioning thyroid pulmonary metastases, to whom 50,000 μc $I^{131}$ was given, reveals no adverse clinical effect four months after the dose was given. In subjects with hyperthyroidism, the thyroid became tender after a dose of 2000 μc when the uptake was over 50 percent. In 33 of 42 such subjects the disease was controlled and the patients returned to normal. In the other 9 the disease was not controlled or the time required for arrest of the disease was too long (over 6 months). One developed myxedema. In successful cases, the average estimated thyroid weight before treatment was 31.2 grams and after treatment it was 13.3 grams. The B.M.R. dropped from an average of +28 percent to one of -9.9 percent. The average amount of protein-bound iodine in the blood dropped from 10.7 to 5.7 mg. percent. (Normal 4 to 7 mg percent). The average dose was 2726 μc$I^{131}$. At first the doses were small (250 μc) and repeated many times. Lately, the usual initial dose has been 2000 μc $I^{131}$. In most patients, a second dose of 2000 uc was given one month after the first dose. In a few cases, up to 4 such doses have been administered. In a very few of the latest cases, 3000 μc or 4000 μc were tried as initial doses.

Further Studies. Blood: Only routine blood studies are available and these have not been adequately followed. There is need for a detailed adequate study. This should be possible now with a hematology technician and space available for this work. Blood proteins: It has been observed by Dr. Trunnell at Memorial Hospital, New York, that after very large doses of radioactive iodine to a patient with functioning metastases from a carcinoma of the thyroid, that one of the effects was a severe drop in the serum albumen. This should be studied in patients receiving smaller doses.

Physical Factors of Measurement. The time required to make routine measurements on patients is very great. An attempt to use counting rate meters has been made in our effort to shorten the time required for individual observations. This has not proved accurate enough for the purpose, up to this time. There is need to make a more adequate study of the effect of distance, filtration, size of standard bottles and size of field of measurement, on the accuracy of measurements of thyroid uptake.

Animal Studies. Detailed studies of organ distribution Of $I^{131}$ in animals should be made. Animal quarters and space to carry out this work have become available to start this work.

Protein Fractionation of $I^{131}$. A study of the rate of rise and total blood content of $I^{131}$ after oral administration of $I^{131}$ should be made. In addition, the program should be expanded by setting up a biochemical laboratory to permit the study of the protein fractionation of $I^{131}$ in

the blood and if possible, in other body fluids. This should give a fuller understanding of the mechanism of iodine utilization and of thyroid metabolism and physiology and perhaps give the best test of significant uptake and action of $I^{131}$.

Effect of Inert Iodine and Antithyroid Drugs on $I^{131}$ Uptake. This important problem has been studied only slightly, because of the difficulty of setting up such experiments in patients. It needs to be pursued in human subjects whenever an opportunity presents itself. Animal experiments to answer this question must also be started.

Throughout this work we have accepted the Oak Ridge calibration of the millicurie.

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PRIVACY ACT MATERIAL REMOVED

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NORMAL

| NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | | | | | | | | 172 | 6.7 | | Normal |
| 2. | | | | | | | | 250 | 17.8 | | Normal |
| 3. | | | | | | | | 250 | 30 | | Normal |
| 4. | | | | | | | | 250 | 34 | | Normal |
| 5. | | | +36 | | 7.94 | | | 250 | 18.8 | | HTCVD - normal |
| AVERAGE | | | | | | | | | 24.46 | | |

PRIVACY ACT MATERIAL REMOVED

PRIVACY ACT MATERIAL REMOVED



NORMAL FUNCTION
WITH THYROID DISEASE

| SE | NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | | | | | | | | | 305 | 8.5 | | NTNG No clin.ev. of toxicity |
| 2. | | | | -8 | | 6.1 | | 152 | 250 | 13.6 | | D.D. Adenoma vs thyroiditis |
| 3. | | | | 19 | | 5.7 | | 187 | 300 | 20 | | NTNG |
| 4. | | | | +18 | | 4.6 | | 189 | 250 | 21 | | NTNG |
| 5. | | | | +2 | | | | 282 | 250 | 21 | | NTNG |
| 6. | | | | -8 | | | | 128 | 250 | 25 | | NTNG (D.D. Hashimoto's Struma |
| 7. | | | | | | | | | 340 | 25 | | NTNG |
| 8. | | | | +25 | | 4.0 | | 252 | 1000 | 26.5 | | NTNG |
| 9. | | | | -4 | | 6.4 | | | 250 | 27 | | NTNG |
| 10. | | | | | | | | | 250 | 28.6 | | NTNG No clin. ev. of toxicity |
| 11. | | | | -13 | | 6.4 | | 158 | 250 | 32 | | NTNG |
| 12. | | | | +12 | | 6.1 | | 173 | 250 | 32.2 | | NTNG |
| 13. | | | | +4 | | 5.8 | | | 210 | 35.6 | | NTNG |
| AVERAGE | | | | +4.7 | | 12.05 | | 190 | | 24.3 | | |





PRIVACY ACT MATERIAL REMOVED

PRIVACY ACT MATERIAL

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| NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | | | -12 | | 5.1 | | 163 | 250 | 3.2 | | Known normal function |
| 2. | | | | | | | | 125 | 5 | | |
| 3. | | | | | | | | 2000<br>2000 | 8<br>6.6 | | Hypothyroid |
| 4. | | | | | | | | 2000 | 8 | | |
| 5. | | | | | | | | 163 | 10.8 | | No clin. ev. of toxicity |
| 6. | | | | | | | | 260<br>2000 | 11.5<br>23.7 | | Clin. ev. of normal function |
| 7. | | | | | | | 269 | 500 | 13.7 | | |
| 8. | | | | | | | 186 | 500 | 14 | | |
| 9. | | | | | | | | 500 | 18.3 | | |
| 10. | | | ≠ 8 | | 6.0 | | 225 | 500 | 20 | | |
| 11. | | | | | 5.6 | | 148 | 2000<br>7000<br>50,000 | 21 | | |
| 12. | | | | | | | | 2000<br>670<br>25,000 | 21<br>11.4<br>16.0 | | |

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CARCINOMA

| NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS Until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 13. | | | | | | | | 2000 | 21.5 | | |
| 14. | | | | | | | | 383 | 22 | | |
| 15. | | | | | | | | 2000 | 27 | | |
| 16. | | | | | | | | 1000 | 31 | | Normal clinically |
| 17. | | | | | 3.9<br>4.5 | | 154<br>176 | 250 | 36 | | |
| 18. | | | | | 6.9 | | 178 | 2000 | 37.6 | | |
| 19. | | | | | 7.5 | | 201 | 2000 | 38 | | |
| 20. | | | | | | | | 1000 | 18 | | No clin. ev. of hypo or hyperthyroidism |
| AVERAGE | | | | | 5.65 | | 189 | | 18.51 | | |

VACY ACT MATERIAL REMOVED





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PRIVACY ACT MATERIAL REMOVED

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GRAVES DISEASE
Treated With $I^{131}$

SATISFACTORY RESULTS

| | NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | 47-F | 40-45 | 15 | +48 | -10 | 14.75 | 4.8 | | 4000 | 60% | 4 mos | |
| 2. | 39-F | 35-40 | 30 | +36 | -22 | 12.0 | 5.1 | | 3000 | 53 | 2½ mos | |
| 3. | 58-F | 30 | 8-10 | +42 | -13 | 9.4 | 5.3 | | 1250 | | 2½ mos | |
| 4. | 25-F | 25 | 10 | +25 | -16 | 9.9 | 4.1 | | 1200 | | 4¼ mos | |
| 5. | 65-F | 25 | 10 | +53 | - 8 | 10.2 | 7.5 | | 3000 | 32.6 | 3 mos | |
| 6. | 48-F | 25 | 5 | +20 | -18 | 9.0 | 6.8 | | 1400 | | 2 3/4 | |
| 7. | 37-F | 30 | 10 | +20 | - 7 | 6.0 | 6.3 | | 4000 | 61 | 1½ | |
| 8. | 17-F | 15 | 5 | +16 | - 3 | 7.2 | 5.4 | | 800 | | 2½ | |
| 9. | 46-F | 40 | 10 | +28 | -12 | | 5.5 | | 3500 | 46.5 | 4 | |
| 10. | 52-F | 30-35 | 10 | +30 | - 4 | 14.3 | 6.2 | | 2000 | | 7½ | |
| 11. | 59-F | 25-30 | 10 | +40 | -26 | 10.0 | 5.5 | | 2000 | 50 | 3 | |



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PRIVACY ACT MATERIAL REMOVED

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PRIVACY ACT MATERIAL REMOVED

GRAVES DISEASE
Treated With $I^{131}$

SATISFACTORY RESULTS

| | NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12. | 29-F | 35 | 10 | +21 | -11 | | 6.9 | | 4000 | 30.5 | 2½ | |
| 13. | 57-F | 35 | 10 | +38 | - 9 | 9.9 | 6.3 | | 4000 | 39 | 4 | |
| 14. | 44-M | 25 | 10 | +22 | | 11.0 | 5.2 | | 2000 | 30 | 2 | |
| 15. | 9-F | 20-25 | 10+ | +22 | | 17.4 | 5.2 | | 2000 | 73 | 3 | |
| 16. | 38-F | 30 | 10 | +26 | - 1 | 12.0 | 5.4 | | 2000 | 68 | 2 3/4 | |
| 17. | 16-F | 30-35 | 15 | +16 | -14 | 12.8 | 7.6 | | 2000 | 65 | 3 | |
| 18. | 26-F | 25 | 10 | +22 | - 6 | 10.1 | 5.2 | | 2700 | | 4 | |
| 19. | 46-F | 30+ | 10 | +13 | - 8 | | 5.4 | | 2600 | 30 | 6 | |
| 20. | 17-F | 35 | 35 | +26 | - 5 | 11.4 | 5.6 | | 4500 | 51.5 | 5 | |
| 21. | 9-F | 25 | 12+ | +2 | -25 | 8.4 | 5.0 | | 3000 | 20 | 5 | |
| 22. | 21-F | 30 | 10+ | +32 | + 6 | 8.0 | 4.6 | | 4500 | 30 | 4 | |

ACT MATERIAL REMOVED



UCRL 41

PRIVACY ACT MATERIAL REMOVED

1175151

GRAVES DISEASE
Treated With $I^{131}$
SATOSFACTORY RESULTS

| | NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOLESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23. | [redacted] 48-M | 35 | 20 | +34 | - 1 | 8.2 | 6.8 | | 1450 | | 4 | |
| 24. | [redacted] 34-F | 30-35 | 15+ | +40 | - 5 | 11.7 | 4.9 | | 3000 | 19.7 | 2 | |
| 25. | [redacted] 16-F | 35-40 | 25-30 | +27 | -13 | 11.9 | 5.2 | | 4000 | 46 | 4 | |
| 26. | [redacted] 32-F | 40 | 10 | | | 9.3 | 6.6 | | 4000 | 12<br>55 | 4 | |
| 27. | [redacted] 56-F | 30-35 | 10 | +43 | - 3 | 9.3 | 6.4<br>8.4 | | 2000 | 84 | 4 | |
| 28. | [redacted] 43-F | 25 | 12+ | +27 | - 2 | 13.8 | 7.0 | | 2000 | 50 | $1\frac{1}{4}$ | |
| 29. | [redacted] 16-F | | | +19 | + 3 | 13.7 | 7.4 | | 1000 | 44 | $4\frac{1}{2}$ | |
| 30. | [redacted] 55-F | 10 | 6+ | +27 | - 5 | 9.7 | 7.9 | | 2000 | 69 | 1 | |
| 31. | [redacted] 41-F | 35 | 15 | +44 | + 7 | 14.4 | 8.4 | | 4272 | 60 | 3 | |
| 32. | [redacted] 26-F | 40 | 20 | +36 | - 2 | On $I^{127}$ | 7.5 | | 6000 | 65 | 5 | PRIVACY ACT MATERIAL REMOVED |
| 33. | [redacted] 24-F | 25-30 | -10 | +20 | +10 | 9.9 | 6.4 | | 3000 | 66 | $3\frac{1}{2}$ | |
| AVERAGE | | 30.0 | 12.1 | +28.3 | -7.2 | 9.8 | 6.3 | | 3104 | | 3.57 | |



UCRL 41

1175152

PRIVACY ACT MATERIAL REMOVED

GRAVES DISEASE
Treated with $I^{131}$

POOR RESULTS

| NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. [redacted] 47-F | 35 | 10-12 | +30 | + 3 | 14.0 | 5.0 | | 4600 | 50 | 16 | |
| 2. [redacted] 33-F | 30 | 15 | +50 | | 13.5 | 7.3 | | 3850 | | 14 | |
| 3. [redacted] 45-F | 45 | 25 | +53 | +22 | 18.6 | | | 3600 | 60 | | Not well at 8 mos.-cannot be traced. |
| 4. [redacted] 41-F | 60 | 35 | +63 | - 7 | 16.0 | 8.4 | | 5400 | 50 | 12 | |
| 5. [redacted] 25-F | 25-30 | 8 | +34 | -12 | 8.0 | 4.6 | | 4700 | 61 | 16 | |
| 6. [redacted] 19-F | 50 | 30 | +34 | +33 | 10.3 | 8.8 | | 9150 | 60 | | Not normal at 1 year. |
| 7. [redacted] 35-F | 50 | 25-30 | +56 | +40 | 14.5 | 7.2 | | 4000 | 62.5 | 2½ | |
| 8. [redacted] 33-F | 40 | 20+ | +23 | -12 | 8.3 | 6.9 | | 9000 | 53 | | Not normal at 1 year. |
| 9. [redacted] 34-M | 30 | 45 | +39 | +23 | 12.2 | 10 | | 8500 | 84 | | Not normal at 6 mos. |
| AVERAGE | 41.1 | 24.3 | +42.4 | +11.25 | 12.83 | 7.28 | | 5867 | 60 | 12 | |

PRIVACY ACT MATERIAL REMOVED

PRIVACY ACT MATERIAL REMOVED

## THYROIDITIS

| NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. [redacted] | | | +27 +21 | | 5.8 | | 170 | 1000 | 3.5 | | |
| 2. [redacted] | | | | | | | | 500 | 4.5 | | No symptoms of hyper or hypo. function of thyroid. |
| 3. [redacted] | | | | | | | | 1000 | 5 | | |
| 4. [redacted] | | | | | | | | 840 | 6.2 | | |
| AVERAGE | | | | | | | | | 4.8 | | |

## TOXIC NODULAR GOITER

| NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | | | +13 -31 | | 10.7 12.7 | | 148 | 220 | 55.4 | | |

PRIVACY ACT MATERIAL REMOVED



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PRIVACY ACT MATERIAL REMOVED

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## HYPOTHYROIDISM

| NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. [redacted] | | | [redacted] | | | | | 250 | 8.1 | | |
| 2. [redacted] | | | | | | | | 250 | 0 | | |

## SPECIAL CASES

| NAME AGE SEX | THYROID WEIGHT Grams Before | After | BMR Before | After | PBI % Before | After | CHOL-ESTEROL | DOSE uc | THYROID UPTAKE % | MONTHS until Normal | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. [redacted] | | | | | | | | 575 | 33 | | Purulent thyroiditis - Stitch abscell. Normal thyroid function clin. |
| 2. [redacted] | | | -13 | | 7.9 | | 118 | 250 | 46 | | Adolescent goiter. |
| 3. [redacted] | | | | | 7.0 | | 161 | 230 | 5.6 | | Progressive exophthalmos. Post-op.thyroidectomy; on thyroid 0/26 daily. |
| 4. [redacted] | | | +16 | | 4.4<br>5.1 | | 200<br>229 | 257<br>230 | 78<br>71 | | Non-toxic goiter |
| 5. [redacted] | | | -16.7 | | 5.4 | | | 250 | 13.7 | | Childhood hypothyroidism - on thyroid, now normal funct. |
| 6. [redacted] | | | +79<br>9-24-46 thyroidectomy<br>-10 | | 13.5<br><br>4.2 | | 129<br><br>233 | 250 | 12 | | Graves Disease, on iodine Rx Low uptake |

PRIVACY ACT MATERIAL REMOVED



UCRL 41

## IV. HEALTH CHEMISTRY

N. B. Garden

Over the past three months the development in equipment and technique indicates that a policy of absolute control over radioactivity can justifiably be set as an ultimate goal. By this it is meant that radioactive material can be stored and processed under such conditions that virtually all escaping or waste particles are trapped and held in absolute control, and any contaminated equipment can be cleaned or disposed of also under absolute control.

Objections have been raised to this policy on the basis that it is unnecessarily severe in some cases and unobtainable in others. However, when the objectors become familiar with the progress being made and with the broad indirect advantages achieved, they usually join in the support of the policy. For the program to be successful it is first necessary to secure cooperation of the workers involved with radioactivity. Otherwise the use of the safest and most efficient equipment would prove a failure. Great progress has been made along these lines of obtaining cooperation during October, November, and December.

The outstanding points which have contributed so greatly toward gaining the confidence of those working with radioactivity are:

1. No contamination.
2. Successful remote process control and manipulating devices.
3. Workable techniques for receiving, storing, transporting, and disposing of active material, whether samples or waste.

"No contamination" refers to the fact that where samples could give off particles that might spread contamination, these are kept in totally enclosed containers until introduced into a controlled work site. This procedure eliminates floor, clothing, and air contamination with a corresponding elimination of personal hazard. The resulting values of mental relief to the worker, the saving in area monitoring and air monitoring, as well as clothes laundering and area decontamination more than offset the expense of the special planning and equipment development required.

Some objectors felt that many workers are concerned with so little activity that no hazard exists and no precautions are necessary. In such cases their investigation usually deals with but a few counts, and although no health hazard exists, a technical, spurious contamination of a few counts may introduce errors of large magnitude into their work. Thus it becomes vital to eliminate this small technical contamination. This becomes more and more true as equipment and technique are developed to do the work without loss of time and with greater efficiency under the no contamination policy.

Under item (2) above, during the period of this report progress has been made in development and standarization of equipment. Particular sucess was achieved with gloved boxes and these have been largely

1175155

standarized together with their fittings and the hoods in which they are used. A glance at the room contamination charts, the hand count charts, the air analysis charts, and the film badge readings lists will give concrete evidence of the lack of the presence of contamination, which is directly attributable to the use of the gloved boxes. The gloved boxes are quite universally used, especially where any appreciable amounts of a alpha activity is involved. Of most recent development, however, is a beta-gamma box, with laminated lead glass window, equivalent in absorptive capacity of 2½ inches of lead.

With the acquisition of a truck for the Health Chemistry Section, the transportation of radioactive materials, such as targets, shipments, etc., and with the development of safe and easily handled target carriers, contamination has been further reduced. The disposal problem is adequately taken care of by the cement-filled drum technique or cement block package. Transportation of waste on the project is carried out exclusively in the Health Chemistry truck, thereby eliminating the possibility of indiscriminate leaks or spills in other project automobiles.

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Information Division

1175156