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MEDICAL AND HEALTH PHYSICS QUARTERLY REPORT

January, February, March, 1954

May 16, 1954

Berkeley, California

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Radiation Laboratory, Department of Physics,
University of California, Berkeley, California

May 16, 1954

THE METABOLIC PROPERTIES OF VARIOUS MATERIALS

Joseph G. Hamilton, M.D.

Tracer Studies

LANTHANIDE AND HEAVY ELEMENTS

Cerium-144

Detailed tracer studies on the metabolism of Ce^{144} in rats are now complete. The experiments presented here are a re-examination of earlier pilot studies with rare earths and were performed for three reasons: first, the number of animals involved in the earlier work was small and the animals were not always uniform as to size and age; second, the techniques were not standardized so that a direct comparison could be made of the different rare earths; and third, some of the radioactive isotopes of the rare earths have only recently become available in high specific activity.

The results of the 1-, 4-, 64- and 256-day studies with Ce^{144} are shown in Table I. There are several general trends which warrant discussion.

(1) The soft tissues other than the liver and kidney initially accumulated less than 0.20% of the dose per gram of wet tissue, but in general the decline in the Ce^{144} content of these tissues was slow, so that by the end of 8 months the Ce^{144} concentration of the spleen had dropped by only a factor of two, and that of the muscle, skin and kidney by a factor of four. The liver initially accumulated 53.7% of the absorbed dose, most of which, 47.2% or nearly nine-tenths, was eliminated in the first 2 months, presumably by the gastrointestinal tract. From the second to the eighth month the Ce^{144} content of the liver dropped by only a factor of two. The large values obtained for the standard error of the mean of the liver Ce^{144} at 64 and 256 days arose from the fact that the individual determinations ranged from 0.9% to 20.4% at 64 days and from 0.24% to 8.1% at 256 days. Apparently there is a large and real individual variation from animal to animal in the release of Ce^{144} from the liver, since the experimental recoveries in these experiments were never less than 90% of the administered Ce^{144} dose, and also when one or more

Table I

The Deposition of Ce^{144} in the Rat 1, 4, 64, and 256 Days after Intramuscular Injection. Values are Corrected for 100 Percent Recovery and are Expressed in Percent of Absorbed Dose. Each of the Five Rats in the 1- and 4- Day Groups Received 20 Microcuries of Ce^{144} and 3.0 Milligrams of Sodium Citrate. The 10 Rats in the 64-Day Group Received 30 Microcuries of Ce^{144} and 4.0 Milligrams of Sodium Citrate. The Five Rats in the 256-Day Group Received 40 Microcuries of Ce^{144} and 6.0 Milligrams of Sodium Citrate. The Standard Error of the Mean for the Liver and Skeleton are Shown at the Bottom of the Table.

	1Day		4 Days		64 Days		256 Days	
	%/org	%/g	%/org	%/g	%/org	%/g	%/org	%/g
Spleen	0.08	0.17	0.10	0.11	0.06	0.11	0.04	0.10
Blood	0.06	0.01	0.01	-	0.01	0.001	0.01	0.001
Liver*	53.7	7.42	51.0	6.57	6.55	0.68	3.31	0.33
Kidney	1.60	0.99	1.45	0.76	0.70	0.34	0.43	0.22
G.I. Tract	0.76	0.15	0.01	0.11	0.23	0.02	0.08	0.01
G.I. Contents	0.63	-	1.77	-	0.09	-	0.02	-
Skeleton**	28.5	1.52	27.7	1.40	19.9	0.89	21.7	0.87
Muscle	1.56	0.02	1.78	0.02	0.81	0.01	0.37	0.01
Balance	4.99	-	2.01	-	0.98	-	1.16	-
Skin	1.26	0.04	1.01	0.04	0.34	0.01	0.22	0.01
Urine	5.77	-	5.95	-	11.2	-	10.31	-
Feces	1.03	-	6.21	-	59.2	-	62.4	-
Injection Site	10.2		6.15		2.75		6.04	
Actual Recovery	98.2		89.6		97.3		100.5	
Std. Error of Mean *	3.1	0.50	0.67	0.18	2.29	0.26	1.3	0.14
Std. Error of Mean **	1.9	0.08	0.95	0.07	0.74	0.04	0.25	0.03

animals in a cage showed high liver retention, the Ce^{144} content of the feces collected from that cage was correspondingly low.

(2) The initial skeletal deposition of Ce^{144}, 28.5% of the dose, is about half that of the liver. However, nearly four-fifths of this appears to be retained for the entire 8-month period. There may be some loss during this time which is masked by skeletal uptake of Ce^{144} released from the liver; however, this process seems to contribute very little to the skeletal Ce^{144} from the second to the eighth month. The drop in the skeletal Ce^{144} concentration from its initial value of 1.52% per gram to 0.87% seems to be more apparent than real, since the animals were young adults when injected, and subsequent skeletal growth would result in a dilution of the Ce^{144} retained.

(3) Except for approximately 10% of the administered Ce^{144} that appears in the urine in the first week after injection, the major portion of the Ce^{144} excreted is found in the feces.

(4) When Ce^{144} is administered intramuscularly as a citrate complex, the absorption from the injection site is very nearly complete in the first 4 days. Further absorption apparently does not occur, since from 4% to 6% of the administered Ce^{144} is found in the injection site 8 months after injection.

Promethium-147

An investigation of the metabolism of the Pm^{147} in the rat over an 8-month period is now under way.

In general the techniques employed are those described in the quarterly report for July, August, September 1953. Pm^{147} separated from a mixture of fission products was obtained from Oak Ridge National Laboratory. The ashed tissue samples were diluted in 2N HNO_3, and suitable aliquots were plated on weighed gold discs. The soft beta particles, 0.223 Mev, were counted with a thin mica-window "Scott Type" G-M tube at maximum geometry.

The results of the 1- and 4- day studies are shown in Table II. Comparing the results obtained with those from studies with Ce^{144}, the following are shown: the soft tissues with the exception of the liver show a somewhat greater accumulation of Pm^{147} than Ce^{144}; the liver initially accumulates about 10% less Pm^{147}; the difference between the skeletal deposition of Pm^{147}, $34.3 \pm 1.6\%$, and of Ce^{144}, $28.5 \pm 1.9\%$, is statistically significant, $p < 0.05$; the urinary excretion of Pm^{147} in the first 24 hours after injection is nearly twice that of Ce^{144}.

Terbium

Studies on the metabolism of terbium in the rat, using Tb^{160} as a tracer, are now complete to 64 days. The Tb^{160} was prepared by bombardment of terbium oxide in the ARCO pile and had a specific activity of 1 mc/mg. The general biological techniques are described in the Quarterly report for July, August and September, 1953. At autopsy the small tissues were placed in weighed porcelain ashing capsules. After incineration the tissue ash was dissolved and spread with 2 N HNO_3,

Table II

The Deposition of Promethium^{147} Complexed with Sodium Citrate in the Rat 1 and 4 Days after Intramuscular Injection. Values are Corrected for 100 Percent Recovery and are Expressed in Percent of Absorbed Dose. Each Rat Received 10 Microcuries of Promethium^{147} and 3 Milligrams of Sodium Citrate. Standard Error for the Mean of the Skeleton and Liver are Shown at the Bottom of the Table.

	1 Day		4 Days	
	%/org	%/g	%/org	%/g
Spleen	0.09	0.19	0.07	0.15
Blood	0.05	0.006	0.01	0.001
Liver*	43.8	6.37	41.4	6.12
Kidney	1.76	1.17	1.44	1.04
G.I. Tract	1.36	0.20	0.63	0.09
G.I. Contents	1.75	-	1.45	-
Muscle	1.98	0.02	0.73	0.008
Skeleton**	43.3	1.82	36.4	2.13
Balance	2.55	-	2.32	-
Skin	1.63	0.05	0.73	0.03
Urine	9.79	-	9.61	-
Feces	0.86	-	5.07	-
Left Leg	4.24		4.75	
Average Recovery	97.6		94.0	
Standard Error of Mean *	1.95	0.35	2.4	0.35
Standard Error of Mean **	1.60	0.12	2.3	0.28

and the dishes were reweighed. The beta particles emitted by Tb^{160} were assayed with a thin-window "Scott Type" G-M tube at about 20% efficiency.

Table III shows the deposition of Tb^{160} in several tissues of the rat 1, 4, and 64 days after its intramuscular administration. Two months after the injection 10% of the administered Tb^{160} still remains at the injection site. It is possible that the amount absorbed depends on both the amount of stable terbium present and the quantity of complexing agent used. Presumably the amount easily absorbed could be increased by either increasing the citrate or decreasing the quantity of stable terbium, or both. It can also be seen that the average experimental recoveries for all three of the time intervals presented are greater than 100%. This is probably owing to an error in the self-absorption curve used.

Comparing Tables I, II, and III, it can be seen that initially (1) the soft tissues contain more Tb^{160} than Pm^{147}; the liver accumulates only about one-third as much Tb^{160} as Pm^{147}; and the skeleton about one and one-half times as much Tb^{160}. Two months after the injection the amount of Tb^{160} in the liver is almost negligible, while the skeleton apparently retains nearly all of the Tb^{160} that it accumulated in the first 4 days. The kidney continues to play an important role in the excretion of Tb^{160} during the entire 2-month period. This is unlike either Ce^{144} or Pm^{147}, in which urinary excretion is apparent only in the first few days after the injection.

A comparison of the pattern of the initial deposition of Ce^{144}, Pm^{147}, and Tb^{160} in the tissues of the rat shows that as the atomic number increases the soft-tissue deposition increases slightly, the liver deposition decreases markedly, and the skeletal deposition and urinary excretion increase markedly. These findings are in keeping with the hypothesis that the decreasing basicity of the trivalent lanthanide rare earth hydroxides with increasing atomic number is apparently one of the factors that determine their metabolic behavior.

Other Rare Earths and Heavy Elements

Long-term studies on the metabolism of $Eu^{152, 154}$, Tm^{170}, and Ac^{227} in the rat are continuing, and will be reported as they are completed. An extensive investigation of the mortality of rats following the injection of various amounts of 11-day Ra^{223}, its effects on the blood picture, and its pathological effects is nearing completion and will be reported in the near future.

Table III

The Deposition of Terbium-160 Complexed with Sodium Citrate in the Rat 1, 4, and 64 Days Following Intramuscular Injection. Values are Corrected for 100 Percent Recovery and Expressed in Percent of Absorbed Dose. Each Rat Received 3 Microcuries Terbium-160, 3 Micrograms Terbium, and 2.8 Milligrams Sodium Citrate. The Standard Error of the Mean for the Liver and Skeleton is Shown at the Bottom of the Table.

	1 Day		4 Days		64 Days	
	%/org	%/g	%/org	%/g	%/org	%/g
Spleen	0.12	0.24	0.13	0.24	0.09	0.17
Blood	0.20	0.02	0.06	0.01	0.01	-
Liver*	15.8	2.23	6.83	0.85	1.09	0.12
Kidney	2.75	1.68	2.05	1.36	0.78	0.42
G.I. Tract	1.43	0.22	0.84	0.13	0.34	0.04
G.I. Contents	2.47	-	0.73	-	0.06	-
Muscle	2.91	0.03	2.31	0.02	1.00	0.01
Skeleton**	53.3	2.44	60.5	2.96	57.1	2.52
Balance	4.66	-	2.70	-	1.70	-
Skin	2.44	0.08	2.10	0.06	0.76	0.02
Urine	11.5	-	15.6	-	21.0	-
Feces	2.48	-	6.17	-	16.1	-
Left Leg	27.2		15.2		10.5	
Average Recovery	112.9		116.5		108.7	
Standard Error of Mean *	0.6	0.11	0.85	0.11	0.26	0.03
Standard Error of Mean **	1.0	0.11	1.6	0.08	0.8	0.05

ASTATINE STUDIES

COMPARISON OF THE ACUTE AND CHRONIC CHANGES PRODUCED IN RATS BY IODINE-131 AND THE ALPHA-ACTIVE ASTATINE-211 (EKA-IODINE) AT LETHAL LEVELS, AND PRELIMINARY CLINICAL DATA UPON THE UPTAKE OF ASTATINE-211 IN PATIENTS SUFFERING FROM THYROID DISEASE

Joseph G. Hamilton, Patricia W. Durbin, and Marshall W. Parrott

Introduction

The first studies with radioactive iodine demonstrated the selective accumulation of I^{128} in the thyroid gland of rabbits.[1*] Subsequently the excretion and uptake of I^{131} by the thyroid gland were studied on patients having different types of disorders of that organ, including thyroid carcinoma. The excretion studies were performed on normal subjects and showed the fraction eliminated to be in the range of 81% to 53% in the first 24 hours following oral administration. These experiments included not only a quantitative determination of the accumulation of I^{131}, but also the stable iodine content of the thyroid gland in various types of goiter. The thyroid tissue was obtained by surgical removal of that organ 24 to 48 hours after the I^{131} was administered.[3] Detailed I^{131} tracer studies in the rat have been made by several investigators, including Johnson and Albert[4] and Hamilton et al.[5]

Apart from the thyroid gland, relatively limited effort has been directed towards a study of acute and chronic effects induced by massive doses of carrier-free I^{131} in experimental animals. A study has been made of the destructive action of I^{131} in the mouse. When the amount administered subcutaneously reached a level of 20 microcuries per gram or greater, the animals usually did not survive for more than one month. This particular experiment was primarily concerned with injury to the thyroid gland and was not devoted to any gross or microscopic pathological changes in other tissues and organs.[6]

Goldberg et al. have made extensive studies in the rat of the acute and chronic effects upon the thyroid gland following large amounts of I^{131}. These investigators employed dose levels up to approximately 5 μc/g on Long-Evans rats, and their period of investigation extended from 3 days to 8 months. They noted that high dose levels produced complete obliteration of the thyroid gland, with some injury to the parathyroid gland. They also observed changes in the pituitary gland, which may be presumed to be the effect of prolonged ablation of functional thyroid tissue.[7] Myxedema has also been demonstrated in thyroidectomized dogs.[8]

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* I^{128} decays with a half-life of 25 minutes, emits beta particles with a maximum energy of 2.02 Mev and a gamma-ray energy of 0.428 Mev. Iodine^{131} decays with a half life of 8.05 days with emission of beta rays, most of which have a maximum energy of 0.608 Mev and an average energy of approximately 0.2 Mev. Beta emission is followed by a complex cascade of gamma rays. The majority of these gamma rays has an average energy of 0.36 Mev.[2]

Element 85, which is a radioactive halogen, was discovered in 1940 and was named astatine by Segrè.[9] Twenty radioisotopes of astatine have now been identified. There are no known stable isotopes of this element. The radioisotope of astatine employed in these experiments is At^{211}, which has a half-life of 7.3 hours.**

The chemical preparation and properties of astatine are very complex. Astatine under certain conditions behaves like a heavy metal such as bismuth, mercury, silver, or antimony.[10] When the first attempts were made to isolate and identify astatine, tracer studies were initiated employing guinea pigs as the experimental animals. In view of the position of astatine in the periodic table, special attention was directed towards the possible selective accumulation of this radiohalogen by the thyroid gland. Control animals and those in which thyrotoxicosis had been induced by the administration of the thyrotropic hormone were used. These animals received both I^{131} and At^{211} at the same time so that a direct comparison could be made between these two radiohalogens in the same tissues and organs. While the accumulation of At^{211} by the thyroid gland in both groups of guinea pigs was roughly a quarter that of I^{131}, this experiment[11] demonstrated a high degree of selective localization and retention of At^{211}. More detailed tracer studies with carrier-free I^{131} and At^{211} were later performed on rats. In these experiments I^{131} and At^{211} were administered intraveneously, and the accumulation of At^{211} by the thyroid gland was observed to be one-tenth that of I^{131} at time intervals ranging from 1 to 72 hours. This type of dual tracer experiment was possible because the alpha particles of At^{211} could be counted in an ionization chamber insensitive to the I^{131} beta particles, which later were measured with a Geiger counter. In this series of experiments the metabolism of astatine in tissues other than the thyroid gland was found to be very similar to that of I^{131} at five time intervals ranging from 1 to 24 hours. The excretion of astatine was observed to be somewhat less than that of I^{131}. The kidney was the principal channel of elimination of At^{211} and of I^{131} as well.[5]

Preliminary studies have been made with At^{211} in the rat at lethal levels. Extensive functional injury to the thyroid gland in the rat was observed by determining the capacity of that organ to subsequently accumulate I^{131}, approximately one month after the administration of the At^{211}. In the thyroids of rats treated with At^{211} a few large and apparently relatively undamaged follicles were observed histologically. This was presumably because the range of alpha particles from At^{211} is of the order of 70 μ, whereas the beta particles of I^{131} have a maximum range of

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** There are two modes of decay for this radioisotope of astatine. 40% of the disintegrations with a half life of 7.3 hours result in the emission of 5.86 Mev alpha particles, and the decay product is Bi^{207}. This radioelement has a half life of 50 years and decays by electron capture accompanied by a complex series of gamma-ray transitions to form stable Pb^{207}. The remaining 60% of the disintegrations of At^{211} have also a half life of 7.3 hours and decay by orbital electron capture to form Po^{211} with the immediate emission of 80-Kev polonium x-rays. Subsequently this radioisotope of polonium decays by the emission of 7.43-Mev alpha particles with a half life of 0.52 seconds to form stable Pb^{207}.[2]

2,000 μ. In this same series of experiments a thyroid gland was secured from a monkey that had received At^{211}. In this instance the degree of injury to the thyroid gland was extreme and not one follicle could be seen on examination of serial sections. However, there were atypical cells present in the peritracheal region which showed radioautographically the capacity to accumulate a tracer dose of I^{131}.[12] This observation in the peritracheal region of atypical cells that were able to accumulate tracer amounts of radioiodine several months after the administration of destructive quantities of I^{131}, has been previously reported.[6] In the experiment employing monkeys, myxedema was demonstrated in one animal that could be somewhat reversed by the oral administration of thyroid substance.[5]

Methods

The rats employed for both the I^{131} and At^{211} experiments were Sprague-Dawley females, 55 days of age and approximately 150 grams in weight at the time the radiohalogen was administered by intravenous injection. The diet employed is similar to "Diet 14" prepared by the University of California Institute of Experimental Biology.[13] The dose levels used for I^{131} were 10, 30, 50, and 70 μc/g, and there were 10, 18, 19, and 20 animals in the groups, respectively. The I^{131} was essentially carrier-free and was obtained from the Oak Ridge National Laboratory, Oak Ridge, Tennessee, U. S. A. These animals were maintained for the first 10 days in metabolism cages with no more than three rats in each cage, and the cages were shielded from each other by one-half inch lead sheet. Space and facilities did not make it feasible to individually isolate each rat to prevent cross-irradiation from one animal to another. In addition, some gamma irradiation was received by these animals from the excretion present in the metabolism cages. In a few instances, it was possible to sacrifice rats that were obviously not going to survive for more than a few hours. This made gross and microscopic specimens available without disturbing the lethality determination. At the end of the first week, the animals were weighed individually in order that changes in weight over an extended period of time could be observed. After 10 days the animals were placed in stock cages in groups of five.

The preparation of At^{211} has been described earlier.[14] At^{211} was administered by intravenous injection at dose levels of 1.2, 1.4, 1.6 and 1.8 μc/g. The number of rats used in these experiments was 18, 30, 20, and 28 respectively. In this series of experiments the problem of cross-irradiation and radiation from excreta can be considered negligible in view of the character of radiations arising from At^{211}. At the end of the first week the surviving animals were weighed and examined periodically. As with the I^{131} experiments, animals which were about to die were sacrificed, and the corresponding gross and microscopic pathological changes were observed. The tissues and organs removed for histological study both in the I^{131} and At^{211} studies included the thyroid gland, adrenals, pancreas, spleen, cervical and mesenteric lymph nodes, liver, lung, and femur.

In order to adequately evaluate the mortality pattern in rats receiving both I^{131} and At^{211}, a probit analysis was made. Extrapolation was necessary to estimate the MLD_{60} values for both radiohalogens. The mathematical procedures employed were those described by Finney.[15]

Two male rhesus monkeys weighing approximately 2.3 kg at an estimated age of 6 months were each given 0.42 μc/g of At^{211} in February 1952. Two additional male monkeys of approximately the same age and weight were maintained as controls. Two female animals of very nearly the same age and weight received 0.8 μc/g of At^{211} in May 1953. As in the study of the rats, the four monkeys that received astatine and the two controls were weighed periodically. Blood counts were taken every 3 to 4 weeks which included erythrocyte count, total white count, differential white count, and hemoglobin determination. A minimum of 500 cells were counted for each differential determination.

The results of this work and earlier studies with astatine indicated that it would be safe to employ this radiohalogen as a tracer in patients suffering from various disorders of the thyroid gland.[5] The main restriction was that the patients be more than 35 years of age. In earlier experiments it was demonstrated that the accumulation of astatine by the thyroid gland of the rat following oral administration was nearly identical to the uptake observed following intravenous or intraperitoneal injection of this radiohalogen, when it was administered 18 hours prior to sacrifice of the animals.[12] The time factor in the clinical studies could not always be controlled as precisely as in the animal work, and ranged from 13.25 hours to 22 hours between the time of oral administration of 50 μc of At^{211} to the patient and the time of extirpation of the thyroid gland. The entire specimen was weighed, and a weighed fraction was left for routine hospital pathological studies. The remainder was brought to the Crocker Laboratory for assay. In each instance a small representative portion of the remaining tissue was taken for histological study. A separate file was maintained for each patient, which included a brief history of the thyroid disorder, a gross description of the tissue specimen obtained, and the clinical diagnosis from the hospital pathologist. After gross examination of tissue specimen, At^{211} was isolated chemically by a modification of a technique employed earlier for the isolation of radioiodine from relatively large amounts of thyroid tissue.[3,16] The accuracy of the chemical isolation of At^{211} was checked by assaying the intact sample with a scintillating-crystal gamma counter that is sensitive to the 80-kilovolt x-rays associated with the radioactive decay of astatine. No such checks were possible for the specimens obtained from two patients who had previously received I^{131}. In several cases both lobes of the thyroid were extirpated, and in one case, a specimen of cervical lymph node was obtained from a patient with papillary adenocarcinoma of the thyroid gland.

Attention should be directed to the time consumed in the chemical isolation of astatine, which may in some instances require more than 6 hours before the assay is completed.

Results

The mortality curve for I^{131} is shown in Figure 1. The MLD_{60} for I^{131} was estimated to be 85 μc/g. It should be noted that the ordinate represents the probit of the percent of mortality and the abscissa the logarithm of the administered I^{131}.

Observations of gross pathological changes in the rats following the administration of I^{131} are at present somewhat limited in scope, but enough animals have been seen so that several reasonably sound generalizations can be made. The animals dying during the first week showed

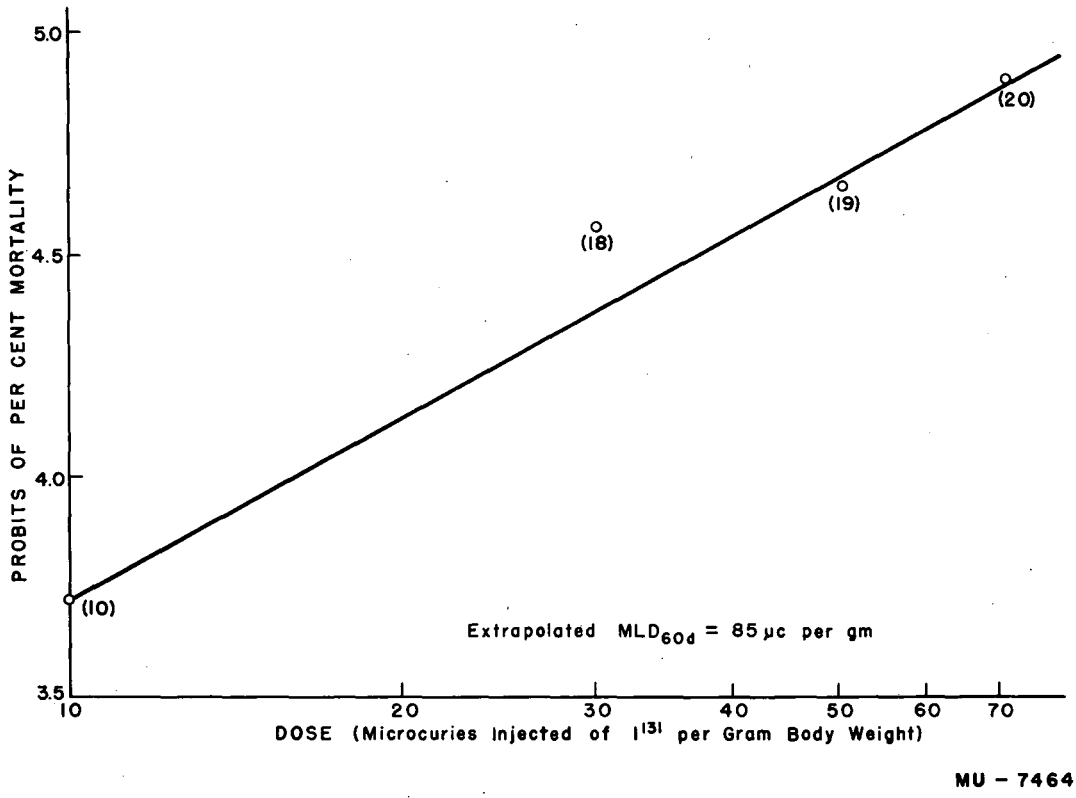

Fig. 1. Probit analysis of the 60-day mortality of Sprague-Dawley rats after a single intravenous injection of I^{131}. The animals used were females, 55 days old when injected. The number of rats at each dose level is indicated by the parenthesized figures beside the experimental points.

very little, grossly, except for somewhat swollen edematous hemorrhagic thyroid glands. At no time was there any evidence of diarrhea. During the second week after administration of I^{131} there appeared grossly to be some moderate changes in some of the lymphatic tissues, including the spleen and thymus, but with relatively little reduction in their size. The thyroid glands were fibrous and greatly reduced in size. Occasionally hemorrhagic areas were noted in the lungs, but these were not extensive in either size or number. During the second and third weeks, the rats receiving 50 and 70 μc/g of I^{131} developed a strange quacking sound associated with respiration, which was presumed to be the result of injury to the larynx and vocal cords. A recording was made of this sound as compared to the normal squeaking a rat makes when slightly hurt. This record was then examined electrically with an oscilloscope. This procedure showed that the treated animals had a very marked change in sound pattern suggesting that the vocal cords may have been striking adjacent tissue which damped out part of the fundamental frequency. The animals that died during the second month following injection grossly indicated very little except that there was no visible evidence of the thyroid gland. Two of the animals apparently died from suffocation, since it was apparent on autopsy that there was almost complete obstruction of the trachea.

The mortality curve of At^{211} for 10 and 60 days is shown in Fig. 2. The MLD_{60} is estimated to be 1.12 μc/g. The pattern of mortality in animals receiving At^{211} was somewhat different from that found in animals given I^{131}. During the initial week, there were relatively few deaths. A large wave of mortality occurred in the second week. As can be seen from Fig. 2, the majority of the animals that survived the second week did not die during the subsequent 50 days. Grossly, the animals that died appeared to be much more severely affected. There was marked emaciation, edema about the eyes, bleeding from the nose, and some diarrhea. The animals usually showed pulmonary hemorrhage, with large amounts of blood in the stomach and small intestines, much of which is presumed to have been swallowed blood from the lungs. The cervical and mesenteric lymph nodes usually were markedly hemorrhagic. The spleen showed from three- to eightfold diminution in size, and after 14 days several spleens were seen in which there were a number of pale nodules approximately 1 mm in diameter. The pancreas, liver, kidney, and ovaries were usually quite pale, which probably arose from the fact that the animals had lost considerable blood. The thymus was very often so much reduced in size that it was difficult to isolate. The thyroid glands in animals dying during this time interval were usually small and frequently showed numerous small hemorrhagic areas. The lacrimal gland in several instances was found to be hemorrhagic. The adrenal glands were often hemorrhagic. Petechial hemorrhages were often seen in the fundus of the stomach but not in the small intestines. Peyer's patches appeared to have been completely obliterated. No gross changes were noted in any other organs. As yet limited information is available on the gross and microscopic changes in animals that died in the subsequent 50-day period following the administration of At^{211}.

Microscopic changes were noted in the lymphatic tissues of animals treated with I^{131} which indicate considerable injury to these structures. A photomicrograph of the spleen from an animal that was sacrificed at 7 days after the administration of I^{131} is shown in Fig. 3. For comparison,

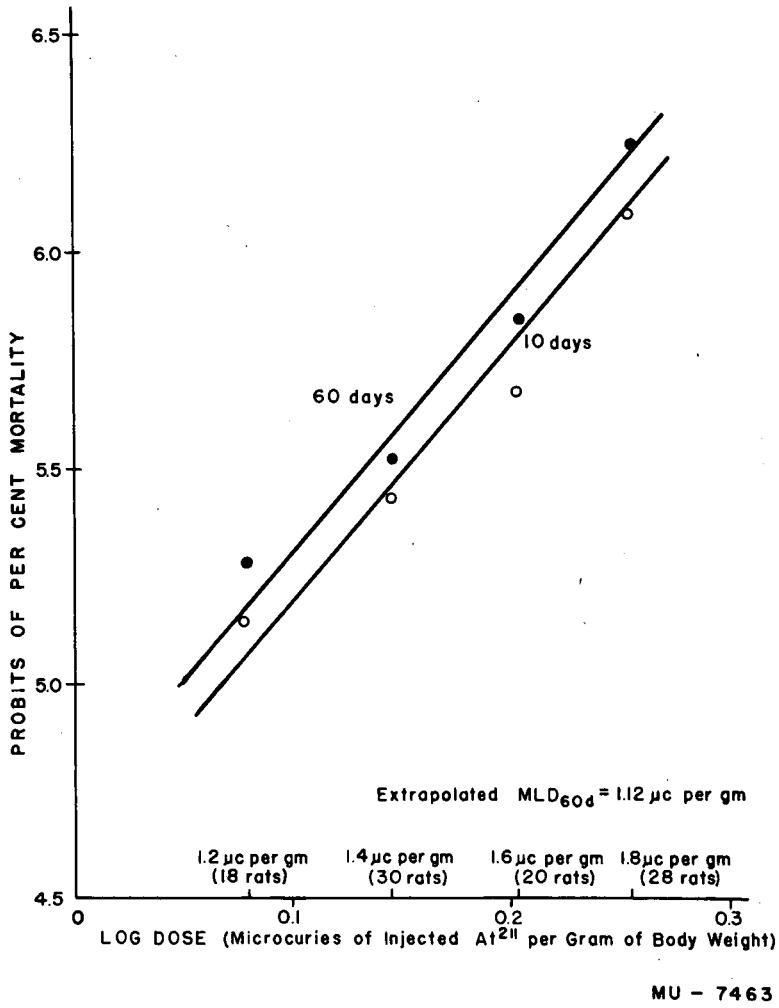

Fig. 2. Probit analysis of the 10- and 60-day mortality of Sprague-Dawley rats after a single intravenous injection of At^{211}. The animals used were females, 55 days old when injected. The number of rats in each group is indicated at the bottom of the plate.

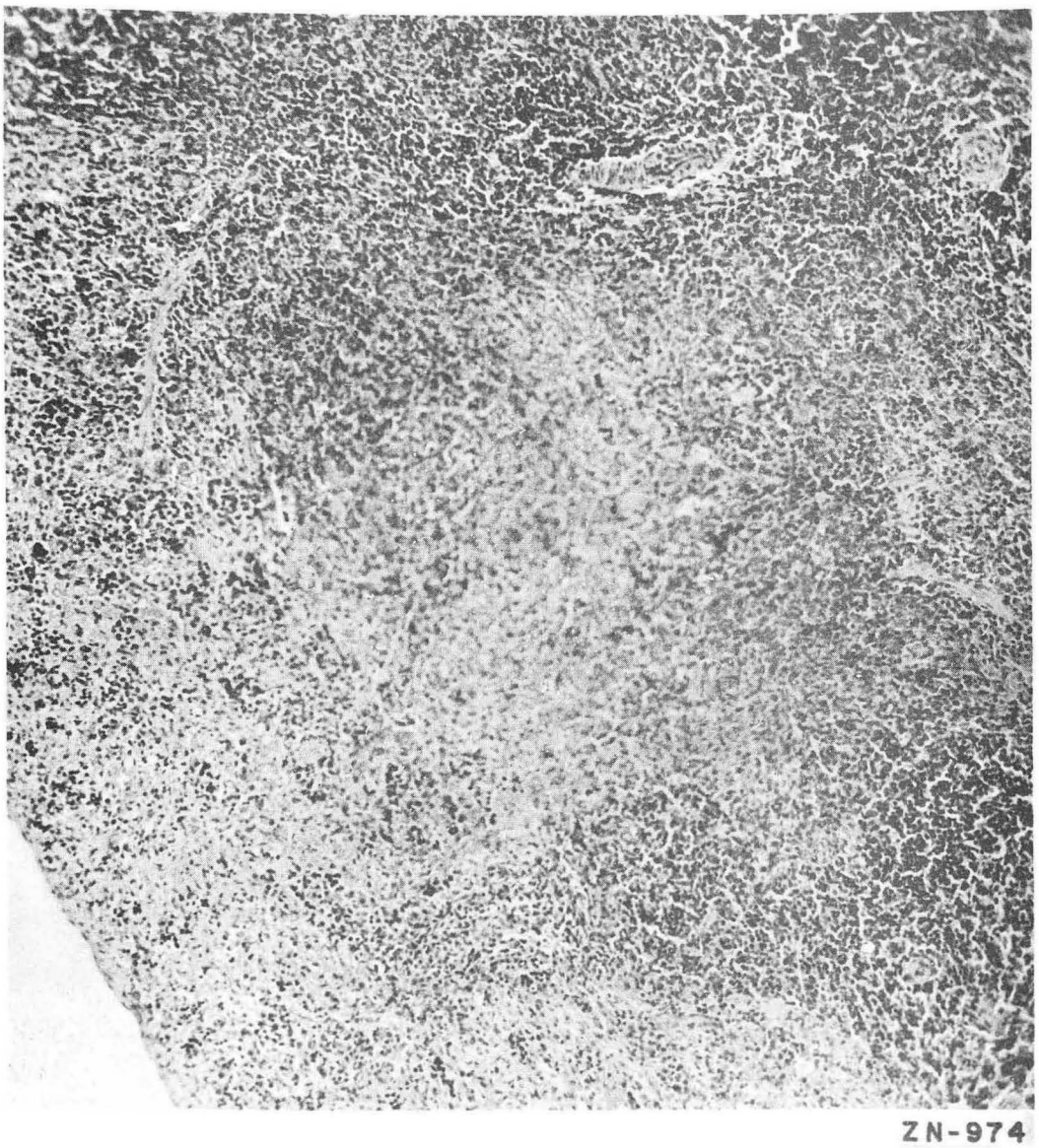

Fig. 3. A section of spleen from a rat that had received 70 μc/g of I^{131} and was sacrificed 8 days later. The marked degree of injury and loss of normal architecture may be seen. Magnification x55. Stain: H and E.

a section of an animal given At^{211} and sacrificed at approximately the same time after administration of the radiohalogen is shown in Fig. 4. A photomicrograph of the spleen of a control animal is shown in Fig. 5.

In an earlier experiment we observed that rats receiving astatine in the range of 4 μc/g show, at the end of a year, marked loss of hair, and retardation of growth from the time of injection, and they obviously are not healthy animals in that they do not maintain the normal degree of body cleanliness that is inherent in this particular strain of rat.

The monkeys likewise show similar changes, including loss of hair, retardation of growth, and apathy, all of which can be attributed to the diminished function of the thyroid gland. The hematological changes observed in the monkey and tabulated in Table I suggest that there is some permanent injury to the hematopoietic tissue, as a permanent anemia and leukopenia have been observed.

The human studies are summarized in Table II. Although the number of patients investigated is small, one striking observation was made. The accumulation of astatine by the thyroid gland in all but one of the patients is quite high; the range extended from 4.6% to 17.8%. The ratio of I^{131} to At^{211} accumulated in the thyroid gland of the rat for these time intervals is approximately 10 to 1.[5] A reasonable prediction of the I^{131} accumulation in the thyroid glands of these patients would be in the range of from 12% to 30%. Thus the selective accumulation of At^{211} in the thyroid gland in this particular group of individuals appears to be significantly higher than would have been predicted from earlier work done with rats.[5]

Discussion

The acute injury and mortality pattern of I^{131} in the rat is not easy to evaluate, since the I^{131} is not uniformly distributed throughout the organs and tissues.[5] The general findings in the acute deaths, however, resemble those seen following lethal doses of x-rays. The microscopic changes in the hematopoietic system, particularly the lymphoid tissues, were not as striking as had been anticipated.

The degree of injury to the vocal cords, larynx, and adjacent structures was not anticipated. These findings are reasonable in view of the tremendous amount of irradiation to that area from the thyroid gland, since the range of the beta particles is sufficient to reach most of these regions. The subsequent severe occlusion of the trachea is a response that can also be attributed to the irradiation from the I^{131} accumulated by the thyroid gland. An appropriate analysis for the mortality of the rat gives a preliminary estimation of the MLD_{60} at 85 μc/g, but many more rats must be given massive doses of I^{131} in order to obtain reasonably accurate values.

Gorbman states that when mice weighing from 20 to 25 g were given I^{131} in amounts greater than 400 μc, they usually died within a month.[6] This would indicate that 20 μc of I^{131} per g in mice was more than 50% lethal in 30 days. In contrast, it was found in the experiments presented here that 85 μc/g of I^{131} in rats produced approximately 50% mortality in 60 days. Thus it would seem that rats are nearly four times less

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Fig. 4. A section of spleen taken from a rat that had received 1.8 μc/g of At^{211} and was sacrificed 6 days later. Here also may be noted the very marked injury and absence of Malpighian corpuscles. Magnification x55. Stain: H and E.

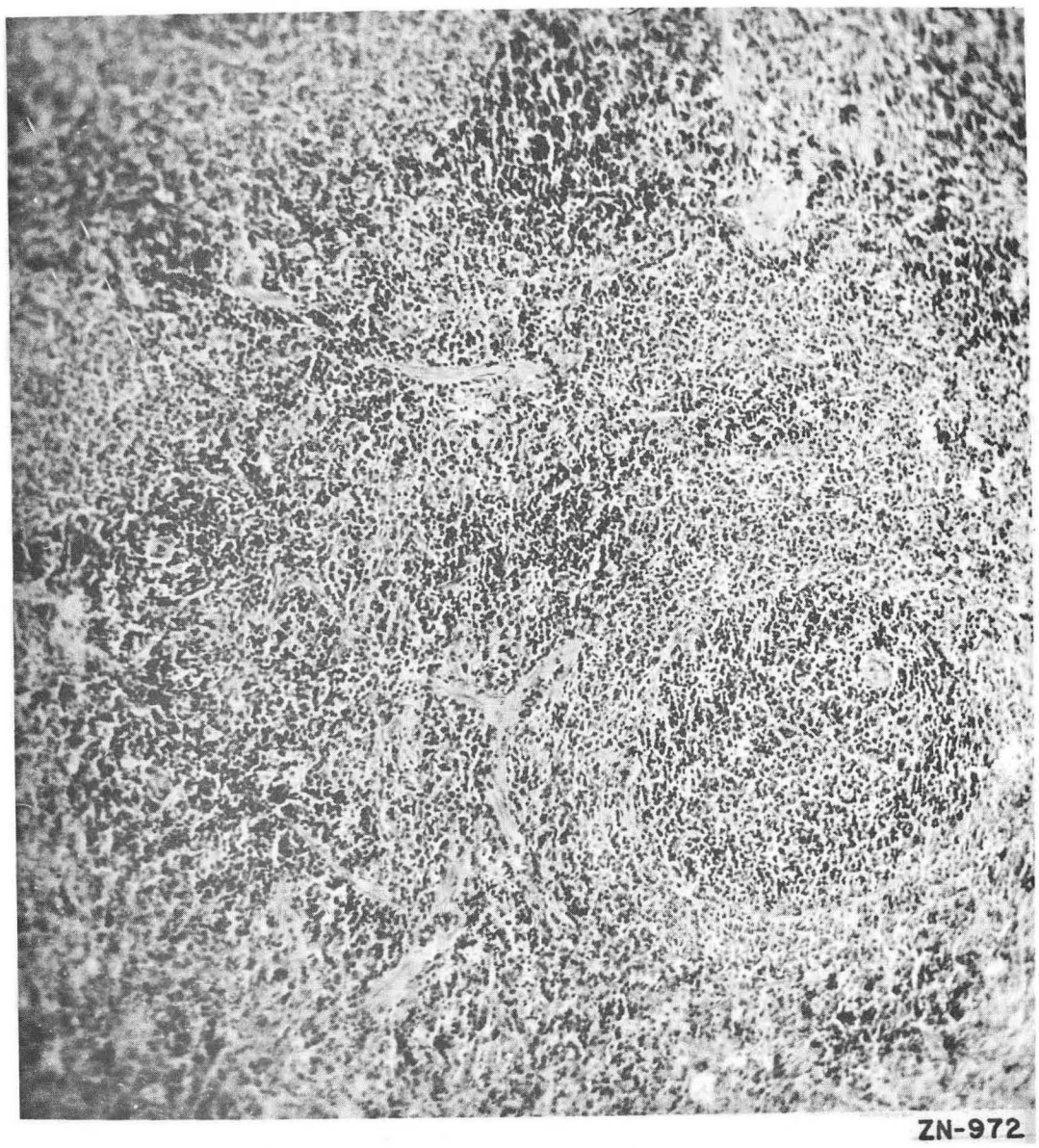

Fig. 5. A section of spleen from a normal rat at the age of 65 days showing very clearly a Malpighian corpuscle. Magnification x55. Stain: H and E.

Table I

The Effect of a Single Intraperitoneal Injection of At^{211} on the Growth and Blood Picture of the Young Rhesus Monkey. The Monkeys Were Six to Eight Months Old When Injected.

Monkey	Sex	Days after injection	At^{211} dose	Body wt kilos	RBC millions/mm^3	WBC thousands/mm^3	Hemoglobin g/100cc	Differential white count	
								Lympho-cytes	Granulo-cytes
#3	M	358	Control	3.32	5.77	14.40	13.8	81.5	18.5
#6	M	358	"	3.92	7.27	9.25	15.8	92.0	8.0
#2	M	358	0.42 µc/g	2.92	3.52	5.75	9.5	73.5	26.5
#5	M	358	"	2.89	3.53	3.30	11.2	85.0	15.0
#1	F	294	0.83 µc/g	2.61	4.66	7.85	11.8	84.0	16.0
#4	F	294	"	3.35	3.56	7.05	10.3	68.0	32.0

Table II

The Uptake of Orally Administered Astatine^{211} (Eka-iodine) by the Human Thyroid Gland in Various Disorders of that Organ

Name	Age	Sex	Thyroid sample	Diagnosis	Hours time	Percent At^{211} in sample	Conc. of At^{211} %/g wet tissue
I. H.	-40	F	Left lobe	Grossly normal	15	5.95	0.54
			Right lobe	" "	18	11.85	1.19
			Cervical lymph node	Papillary adenocarcinoma	18	<0.01	<0.001
C. A.	41	F	Right lobe	Nontoxic metaplasia	13-1/4	2.85	0.27
E. B.	31	F	Whole gland	Nontoxic nodular goiter with cyst formation	16-1/4	6.75	0.55
D. M.	35	F	Whole gland	Toxic goiter (lugolized)	15	6.66	0.21
H.	52	M	Right lobe	Graves' disease (Thyroxine, lugolized)	18	0.172	0.017
T. A.	43	F	Left lobe	Nontoxic nodular goiter	14	6.55	0.26
C. W.	56	M	Left lobe	Grossly normal	13-1/2	4.90	0.39
			Right lobe	Nontoxic nodular goiter	13-1/2	2.56	0.024
R. C.	68	M	Whole gland	Nontoxic nodular goiter	22	4.61	0.021

sensitive to I^{131} than are mice. This differential effect may be owing in part to the fact that the rat has a tendency to have a fuller digestive tract, which will render the I^{131} beta particles less effective in the irradiation of the gastrointestinal tract because of self-absorption.

The striking acute effect of lethal amounts of At^{211} when given to the rat are difficult to interpret. The organs and tissues in which hemorrhage was most obvious upon both gross and microscopic examination include spleen, lymph nodes, lung, and adrenal. An earlier experiment indicated that these four organs had the greatest relative selectivity for At^{211} as compared to I^{131}.[5] The massive hemorrhage observed in these organs may have been owing to increased capillary fragility.

The chronic changes in the survivors of lethal amounts of At^{211} are even more difficult to interpret, because there are two independent actions of this radiohalogen. Most of the changes seen in the rat can be directly attributed to an endocrine imbalance owing to the essentially complete ablation of the thyroid gland. The persistent anemia and leukopenia very probably are due at least in part to the irradiation of the hematopoietic system. The chronic changes in the blood picture and general condition of the monkey are quite similar to those observed in the rat, and here again one is faced with the problem of differentiating between the effects of the lack of thyroid hormone and the action of a relatively large amount of ionizing radiation given over a short period of time.

Summary

1. The acute and chronic effects of lethal amounts of I^{131} and At^{211} have been studied in the rat.

2. A probit analysis for the mortality of I^{131} and At^{211} in the rat is presented.

3. The acute, gross and microscopic changes in At^{211} in the rat have been observed in considerable detail.

4. The chronic changes following administration of large amounts of At^{211} in the rat have been investigated. There appear to be changes owing to the absence of appreciable amounts of the thyroid hormone as well as radiation effects.

5. Chronic changes have been observed in monkeys receiving At^{211}. The effects appear to be related both to endocrine imbalance resulting from radiothyroidectomy and to apparent radiation injury.

6. A limited number of uptake studies of At^{211} have been done with patients suffering from various disorders of the thyroid gland, including carcinoma. There was no accumulation of At^{211} in a metastatic carcinoma of the thyroid gland. The accumulation of At^{211} in the thyroid gland in this series of patients appeared to be relatively greater than was observed in the much larger number of rats.[5]

Acknowledgments

This document is based on work performed under the auspices of the U. S. Atomic Energy Commission. The production of the astatine was the responsibility of Mr. G. Bernard Rossi and the staff of the 60-inch cyclotron. Discussions with Dr. Warren M. Garrison were most helpful for the development of procedures for the isolation of astatine from human thyroid tissue. A large share of the effort of certain phases of the experiments presented in this paper were due to the invaluable assistance of Miss Margaret Gee, Miss Nylan Jeung, Miss Marilyn Hemenway and Mrs. Ruth Newman. The sound studies were done by Mr. Boyd Weeks. The histological specimens were prepared by Miss Muriel Johnston. The assistance in the preparation of the manuscript by Mrs. Barbara Butler and Miss Billie Kelso was invaluable.

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FORTHCOMING REPORTS

Four papers are being prepared on different phases of work with At^{211} and will subsequently be reported.

1. A Modified Method of Preparing Astatine Solutions Suitable for Animal Injection.

2. Preliminary Clinical Studies on the Accumulation of Astatine-211 by the Human Thyroid Gland.

3. The Effect of Pretreatment with Propyl Thiouracil on the Accumulation of Astatine-211 by the Thyroid Gland of the Rat.

4. The Accumulation and Destructive Action of Astatine-211 (Ekaiodine) in the Thyroid Gland of Rats and Monkeys.

RADIATION CHEMISTRY

Warren M. Garrison, Winifred Bennett, Sibyl Cole,
H. Ralph Haymond, and Boyd M. Weeks

During the past quarter, a major part of our activity has been involved in the bombardment of samples for storage in anticipation of the projected temporary shutdown of the Crocker 60-inch cyclotron. Most of the irradiations were made to obtain additional information on the acetic acid–water and glycine–water systems. Some of these data are included in the present report, together with additional evidence for the identification of products formed in the irradiation of dilute formic acid solutions. A summary report of the acetic acid work will appear in the forthcoming quarterly.

Acetic Acid (Oxygen-Free Systems)

Winifred Bennett, Sibyl Cole, H. Ralph Haymond, and Boyd M. Weeks

In previous reports[1,2] it has been shown, for heavy-particle irradiation of acetic acid–water systems, that

(1) Hydrogen, hydrogen peroxide and succinic acid are the principal products of the indirect action of radiation in "dilute" acetic acid solutions at radiation doses below 1×10^{20} ev/cm^3.

(2) The relative yields of hydrogen, hydrogen peroxide, and succinic acid in dilute acetic acid vary with the specific ionization of the incident radiation in a manner consistent with current theories of radiation decomposition of water.[3]

(3) The radiation yields (G values)[4] of these products increase with acetic acid concentration in the range 0.0625 to 1.0 M. With increasing acetic acid concentration above 1.0 M, a continuous decrease in G value for hydrogen, hydrogen peroxide, and succinic acid is observed. Values for the latter two products decrease essentially to zero at 16 M acetic acid.

(4) Radiation yields of other products--including carbon dioxide, methane, ethane, and carbon monoxide--increase continuously with acetic acid concentration from 0.0625 to 16 M acetic acid. With the possible exception of ethane, G values for these products show a linear dependency on acetic acid concentration.

Radiation yields obtained with 35-Mev helium ions and 18-Mev deuterons for acetic acid solutions 0.0625 M to 16 M are compared in Fig. 1 and Fig. 2. Processes occurring in the radiolysis of dilute acetic acid may be represented in brief by

$$H_2O \longrightarrow H + OH, \qquad (1)$$

[1] Quarterly report, UCRL-2243, Jan., Feb., Mar. 1953.
[2] Quarterly report, UCRL-2111, Oct., Nov., Dec. 1952.
[3] Discussions Faraday Soc. 12, 155 (1952).
[4] Number of molecules formed per 100 ev absorbed energy.

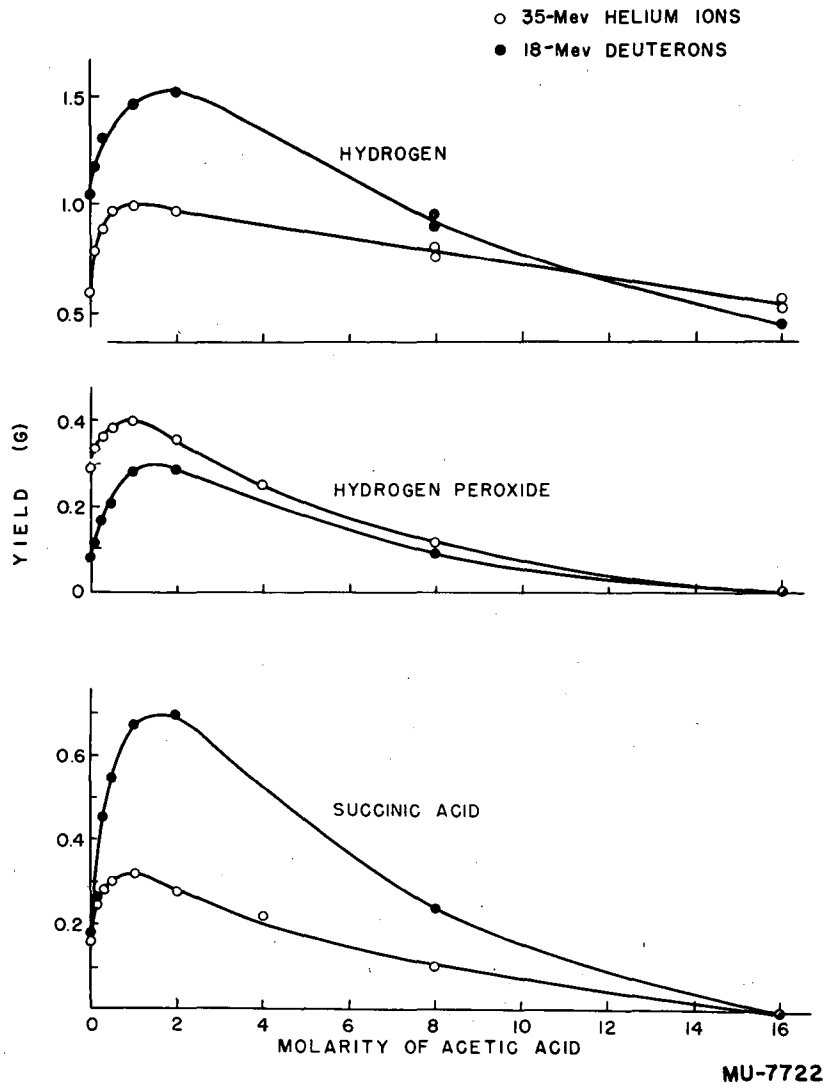

Fig. 1. Radiation yields of hydrogen, hydrogen peroxide, and succinic acid as a function of acetic acid concentration. Beam intensity, 0.2 μa; dose, 0.1 μah; target volume, 100 ml.

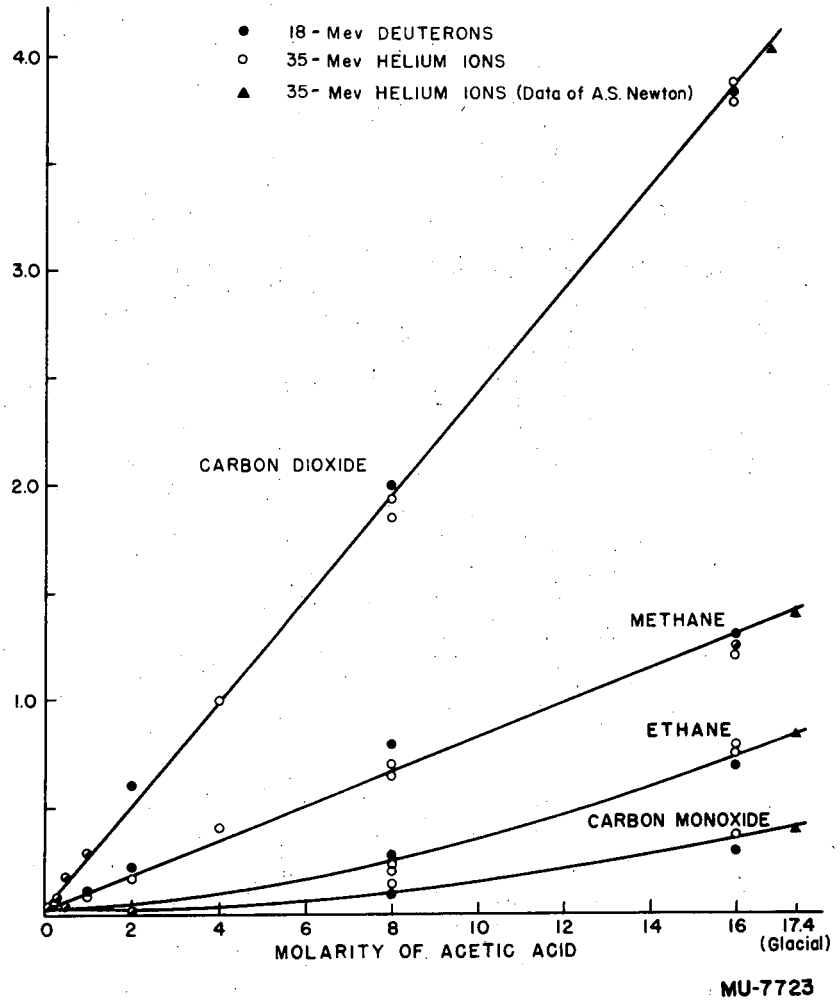

Fig. 2. Radiation yields of carbon dioxide, methane, ethane, and carbon monoxide as a function of acetic acid concentration. Beam intensity, 0.2 μa; dose, 0.1 μah; target volume, 100 ml.

$$H_2O \longrightarrow 1/2\ H_2 + 1/2\ H_2O_2; \quad (2)$$

$$OH + CH_3COOH \longrightarrow CH_2COOH + H_2O, \quad (3)$$

$$H + CH_3COOH \longrightarrow CH_2COOH + H_2, \quad (4)$$

$$2CH_2COOH \longrightarrow (COOH)\ CH_2\ CH_2\ COOH, \quad (5)$$

$$OH + H_2 \longrightarrow H_2O + H, \quad (6)$$

$$H + H_2O_2 \longrightarrow H_2O + OH, \quad (7)$$

where (1) and (2) represent the radiation decomposition of water. Reaction (1) represents[5] the formation of H and OH radicals, which diffuse out of the particle track and are available for reaction with solute molecules. Reaction (2) represents the fact of H and OH radicals formed in high concentration in spurs or "hot spots".[3] Reactions (1) and (2) are considered as two independent primary radiation processes. In the absence of added solute, radicals formed in (1) react with the products of (2) via (6) and (7). The number of radicals involved in (6) and (7) decreases with increasing acetic acid concentration as competing reactions (3) and (4) become important. The radiation yields of hydrogen, hydrogen peroxide, and succinic acid accordingly increase with acetic acid concentration. The G value for succinic acid reaches a maximum with 35-Mev helium ions at an acetic acid concentration of 1.0 to 2.0 M. This corresponds to the case in which all the available OH radicals disappear by reaction (3). Corresponding data obtained in irradiations with 18-Mev deuterons give a larger maximum G value for succinic acid in accordance with the observation that the relative number of water molecules decomposed via (1) as compared to (2) increases with decreasing specific ionization of the incident radiation.

As the acetic acid concentration is increased there is a corresponding increase in the fraction of total energy absorbed by direct interaction with acid molecules. The observed decrease in succinic acid yield with increasing acetic acid concentration is attributable to the fact that a decreasing fraction of the total energy is dissipated via reactions (1) and (2). The relationship between acetic acid concentration and radiation yield for carbon dioxide, methane, ethane, and carbon monoxide (Fig. 2) indicates that these products are formed principally by reactions induced by direct interaction of the radiation with acetic acid molecules throughout the entire concentration range, i.e. from 0.0625 to 16 M. Almost identical G values for these products were obtained with 35-Mev helium ions and 18-Mev deuterons.

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[5] A. O. Allen et al., J. Phys. Chem. 56, 575 (1952).

A series of studies has been initiated to obtain information on the nature of the intermediate species involved in the formation of the gaseous products derived from acetic acid. One method that is being employed is based on the fact that certain substances such as iodine, oxygen, styrene, and catechol, if present in the irradiated acetic acid–water systems, may react preferentially with radiation-produced radical intermediates. Preliminary results on the effect of these substances on product gas yields from 16 M acetic acid are summarized in Table I. The radiation yields of methane, ethane, and hydrogen are considerably lower in irradiation solution containing a "radical trap". Carbon dioxide and carbon monoxide yields remain substantially the same. These effects will be discussed in detail in a forthcoming report.

Effects of Oxygen in the Irradiation of Aqueous Acetic Acid

H. Ralph Haymond

Further evidence has been obtained that glycolic acid is a product of the irradiation of oxygenated aqueous acetic acid. A colorimetric method for the determination of glycolic acid in target solutions has been described previously. Other nonvolatile acid products have been isolated and quantitatively measured by in vacuo distillation of the acetic acid followed by chromatography of the nonvolatile residue. These methods are unsatisfactory for the glycolic acid because the amounts of glycolic acid produced are near the lower limit for identification by our chromatographic methods, and glycolic acid is partially volatile, either by steam distillation or by sublimation after the liquid has been removed. In order that the identification and measurement of glycolic acid would not depend entirely on the colorimetric method the following experiments were done.

Sixty ml of 1 M acetic acid containing approximately 200 μc of 1-C^{14}-labeled acetic acid was irradiated with 35-Mev helium ions at a beam intensity of 0.1 microampere for 0.05 microamperehour. The C^{14}-acetic acid was previously purified by in vacuo distillation of neutral volatiles followed by distillation of the acetic acid in vacuo. After irradiation, 30.4 mg of glycolic acid was added to 45 ml of the target solution, and the solution was distilled to dryness in vacuo. The nonvolatile residue, containing a part of the glycolic acid, was chromatographed on a silica gel column. Column dimensions were those of our previously reported standard column. The aqueous phase was 0.5 N HCl, and all solvent mixtures were saturated with 0.5 N HCl. The following sequence of solvents was used in method I.

220 ml of 5% butanol – 95 % $CHCl_3$ v/v

300 ml of 12.5% butanol – 87.5% $CHCl_3$ v/v

300 ml of 20% butanol – 80% $CHCl_3$ v/v

This sequence of solvents is known to separate glycolic acid satisfactorily from acetic, succinic, glyoxylic, and oxalic acids. Ten ml samples of the effluent solvent were titrated with 0.01 N NaOH as previously described.

At the glycolic acid titre peak there occurred a corresponding peak

Table I

Effect of Some Added Solutes on Product Gas Yields from 16 M Acetic Acid Radiation, 35-Mev He^{++}; Beam Intensity, 0.05 μa; Target Volume, 100 ml; Solution, 16 M CH_3COOH; Dose, 0.0125 μah.

Run	Solute	Radiation Yields (mol/100 ev) H_2	CO_2	CH_4	C_2H_6	CO
1	None	0.56	3.72	1.15	0.83	0.25
2	"	0.54	3.88	1.17	0.84	0.25
3	0.05 M I_2	0.39	3.70	0.58	0.45	0.29
4	"	0.39	3.84	0.58	0.42	0.32
5	0.5 atmos. O_2	0.48	4.28	0.78	0.72	0.26
6	"	0.50	4.14	0.77	0.67	0.27
7	0.25 M Catechol	0.43	3.60	1.09	0.69	0.29
8	"	0.46	3.81	1.15	0.69	0.29
9	20% styrene, v/v	0.32[a]	3.20	0.59	0.51	0.24
10	"	0.31[a]	2.82	0.51	0.40	0.24

[a] Yields calculated on basis of energy absorbed in acetic acid estimated by Bragg approximation.

of C^{14} activity, as shown in Fig. 3. The fraction of total glycolic acid that was not volatile was calculated from the known amount of glycolic acid added before distillation and the total amount in the titre peak, and the yield of glycolic acid from the irradiation was calculated from the total C^{14} activity in the peak and the calculated fraction that was not volatile. The radiation yield obtained in this manner agreed with that obtained by a colorimetric determination of glycolic acid in the same target solution. To further confirm this method the samples from the glycolic acid peak were combined and chromatographed, after removal of the solvents by distillation in vacuo, by a different method (II), in which the only solvent was 30% iso-butanol - 70% $CHCl_3$ saturated with 0.05 N HCl. There was a correspondence between titre and activity by this method also (Fig. 4). The entire procedure, including irradiation, was repeated through the first chromatographic method and yielded similar results. A control experiment in which all steps except the irradiation were carried out showed no C^{14} activity in the glycolic acid peak.

Studies on some effects of added solutes, acetic acid concentration, and total dose on the oxygen–acetic acid system are being continued.

Formic Acid (Oxygen-Free Systems)

Sibyl Cole and Winifred Bennett

In a previous quarterly report[6] it was shown by partition chromatographic methods that three nonvolatile acids are produced in the helium-ion irradiation of 0.25 M formic acid solutions at radiation doses in the order of 10^{20} ev/cm^3. Recent work on 0.25 M solutions containing $HC^{14}OOH$ has shown that the major peak corresponds to tartronic acid, (COOH)-CHOH-COOH. Evidence for this identification is based on an observed correspondence between the appropriate product activity and the titre of added authentic tartronic acid in two different partition-chromatographic procedures involving silicic acid columns. The co-chromatographs were developed with 35% n-butanol - 65% chloroform (Fig. 5) and 35% n-butanol - 65% chloroform saturated with 0.5 N sulfuric acid (Fig. 6). The details of the chromatographic procedure have been reported.

Glycine (Oxygen-Free Systems)

Boyd M. Weeks

Various aspects of the current study of the radiation chemistry of aqueous glycine solutions have been discussed in previous quarterly reports beginning with UCRL-2111, October, November, December 1952. Work in the past quarter has been directed primarily toward the preparation and irradiation of a series of inert as well as C^{14}-labeled glycine targets, and a beginning has been made on the analysis of the products formed.

All targets employ glycine (Nutritional Biochemicals Corp.) recrystalized several times from doubly distilled water. The glycine so prepared

[6] Quarterly report, UCRL-2243, Jan., Feb., Mar. 1953.

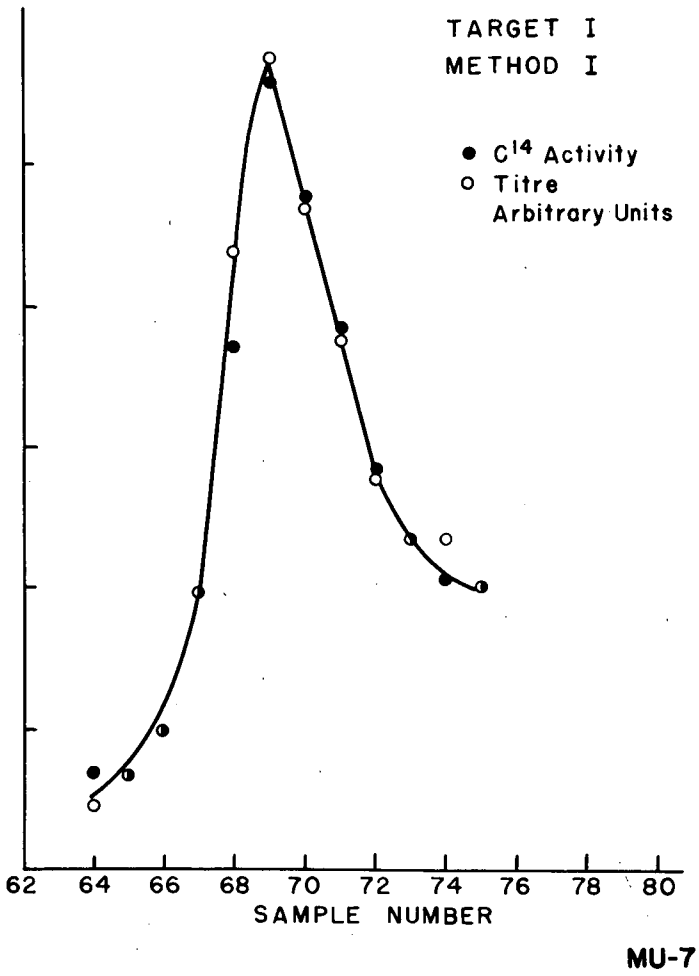

Fig. 3. Co-elution of authentic glycolic acid with C^{14}-labeled product formed in irradiation of 1.0 M acetic acid containing $CH_3C^{14}OOH$. (Method I)

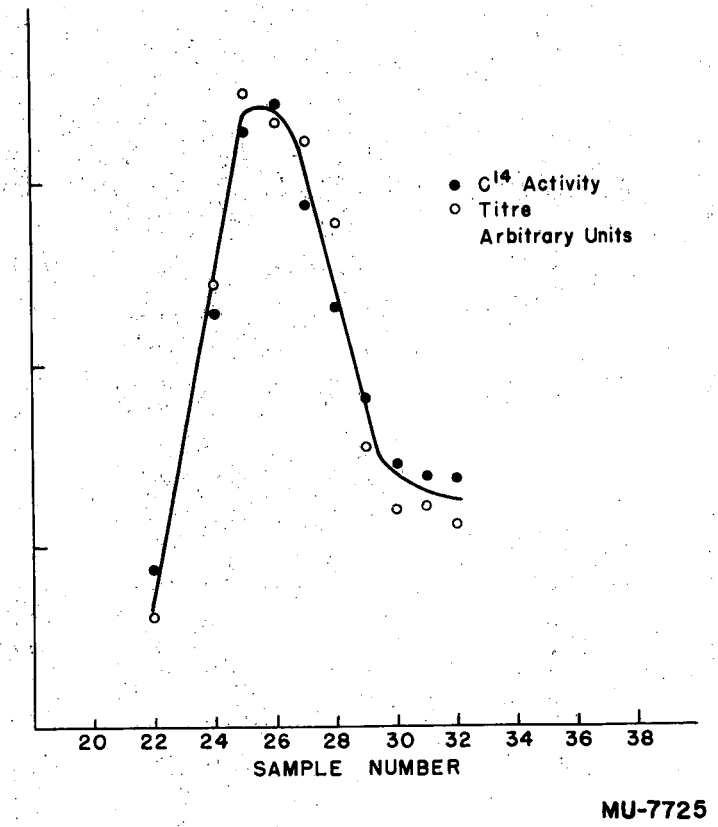

Fig. 4. Co-elution of authentic glycolic acid with C^{14}-labeled product formed in irradiation of 1.0 M acetic acid containing $CH_3C^{14}OOH$. (Method II)

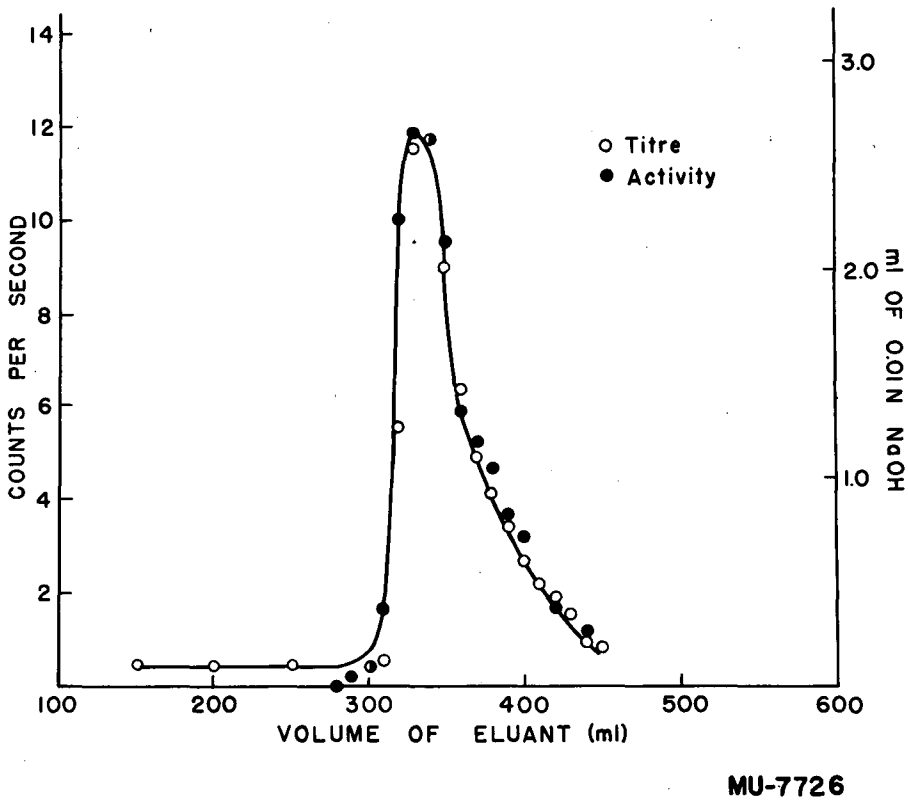

Fig. 5. Co-elution of authentic tartronic acid with a nonvolatile C^{14}-labeled acid (II) formed in irradiation of 0.25 M formic acid containing $HC^{14}OOH$. (Eluant, 35% n-butanol — 65% chloroform)

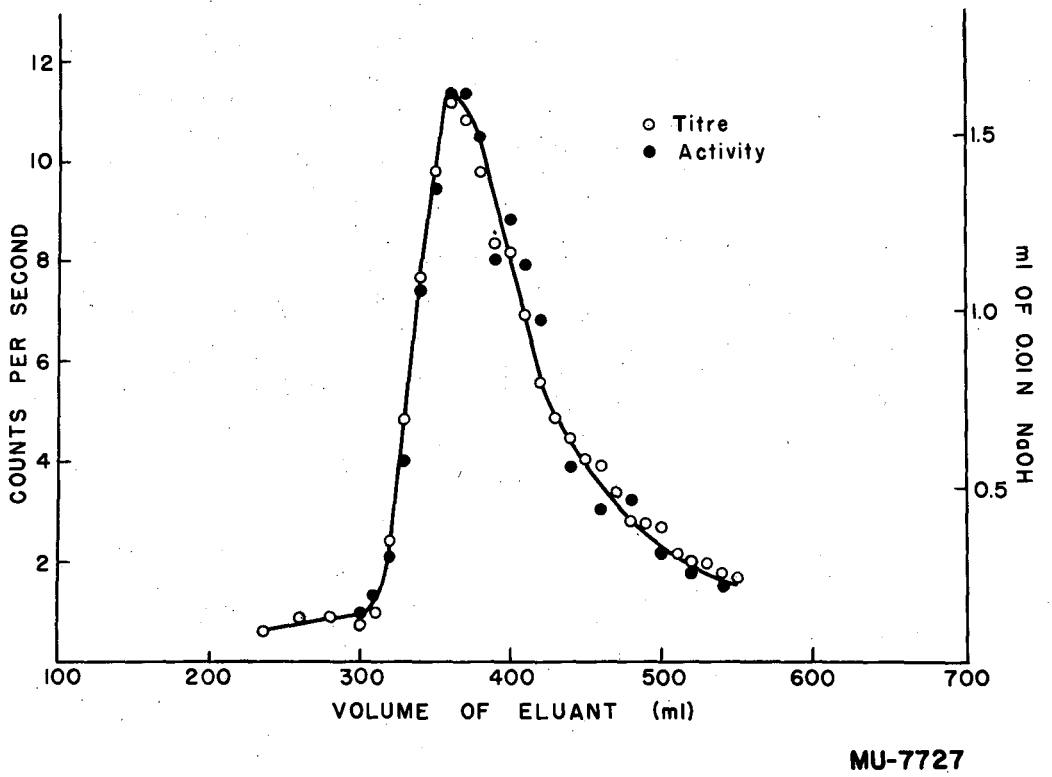

Fig. 6. Co-elution of authentic tartronic acid with a nonvolatile C^{14}-labeled acid (II) formed in irradiation of 0.25 M formic acid containing $HC^{14}OOH$. (Eluant, 35% n-butanol — 65% chloroform saturated with 0.5 N sulfuric acid)

is stored in the dark until just before use, when it is dissolved to the proper concentration in doubly distilled water. All targets (except the C^{14}-labeled targets) are of the sealed, evacuated, Erlenmeyer flask type (described in detail in connection with the acetic acid work). About 100 ml of solution is irradiated at a time and provision is made for agitation of the solution during irradiation. Cyclotron-accelerated He^{++} ions of about 35 Mev at a dose rate of 4×10^{22} ev/hr (corresponding to a cyclotron beam current of 0.2 μa) are used throughout.

Two series of irradiations were undertaken. One series employed 0.25 M glycine solutions, for which the dose was varied from 3×10^{19} ev/ml to 1×10^{21} ev/ml. In the other series a constant dose of 1×10^{20} ev/ml was given but the glycine concentration was varied from 0.0625 M to 3.3 M.

Two C^{14}-labeled targets were also prepared and irradiated as follows: about 200 μc of C^{14}-labeled glycine were added to enough carrier glycine (prepared as described above) to provide a 0.25 M solution when dissolved in 10 ml of water. In one target the glycine was labeled in the methyl position, in the other the carboxyl position was labeled. Each target was given a dose of 4×10^{20} ev/ml in one of the small fritted-disc target cells already described in connection with the acetic acid work. The target solution was agitated and kept free of O_2 during irradiation by a stream of argon bubbling through the fritted disk provided for that purpose.

The analysis of the irradiated solutions follows the procedures outlined in detail in previous reports. Briefly the procedure is as follows: gaseous products are identified and determined mass-spectrometrically.[7] H_2O_2 is determined by titration with $Ce(HSO_4)_4$. Nitrogen bases and amino acids are isolated by ion-exchange chromatography and determined by direct titration of the hydrochloride salts with sodium hydroxide. Organic acids are isolated by silicic acid chromatography and determined by titration with sodium hydroxide. Methods for isolating and determining the nonacidic, nonnitrogen products are being developed. Figures 7 - 10 show typical elution curves for ion exchange and silicic columns.

Identification of products and the determination of yields is as yet incomplete, but the following table shows progress so far made in this direction. All targets were 0.25 M glycine irradiated in evacuated cells. The dose was in all cases 4×10^{20} ev/ml at a dose rate of 8×10^{22} ev/hr.

In the dose-yield and concentration-yield studies only a portion of the analyses have been completed. Figure 11 shows the effect of varying the glycine concentration on hydrogen, carbon dioxide, and carbon monoxide yields.

Work on further identification of products, as well as additional dose-yield and concentration-yield data collection, is now in progress.

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[7] All mass spectrometric data were obtained through the cooperation of Dr. Amos Newton.

Table II

Product	G $\frac{\text{Molecules produced}}{\text{100 ev absorbed}}$	Evidence for identity and method of determination	No. of targets analyzed
H_2	0.7 - 0.9	Mass spectrometer	8
CO_2	0.3 - 0.4	Mass spectrometer	8
H_2O_2	0.12 - 0.15	$Ce(HSO_4)_4$ titration	8
CH_3COOH	0.04 - 0.05	Silicic acid chromatography, mass spectrometer	4
HCOOH	0.05 - 0.06	Silicic acid chromatography, mass spectrometer	4
NH_3	0.75	Ion exchange chromatography, titration curve, Nessler's reagent, absence of carbon	3
CH_3NH_2	0.08	Ion exchange chromatography, titration curve, absence of carbon, mass spectrometer	3
A (Fig. 8)	0.045	Unidentified, isolated by ion exchange chromatography	3
B (Fig. 8)	0.075	Unidentified, isolated by ion exchange chromatography	3

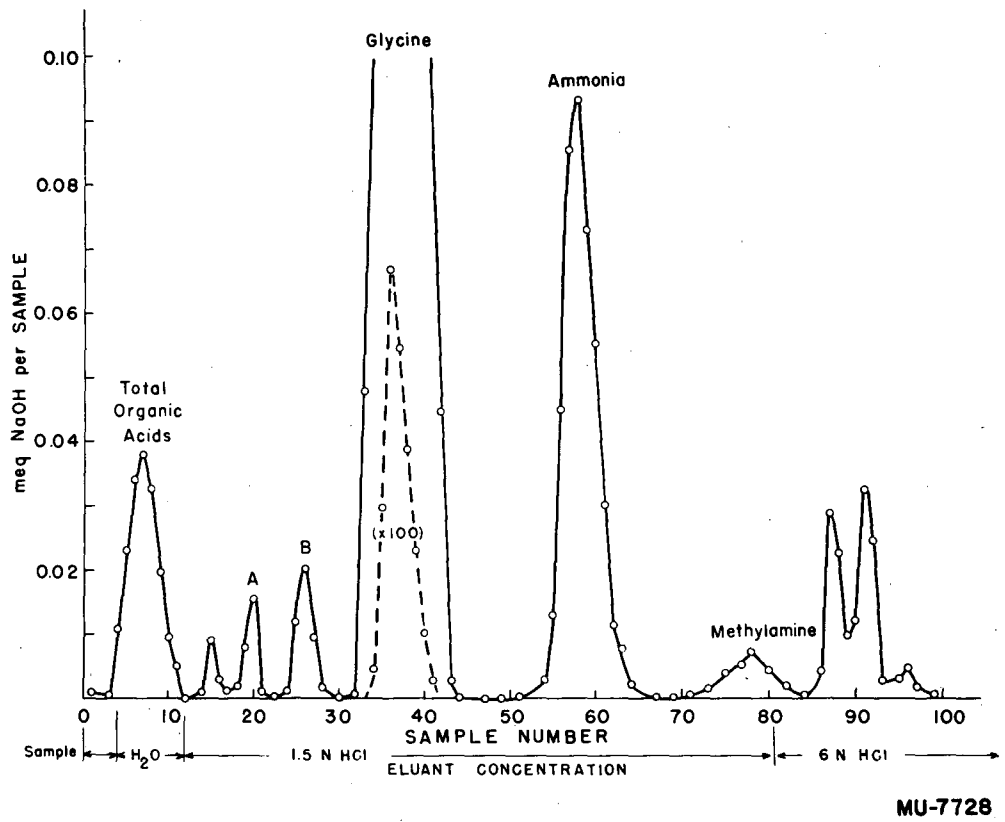

Fig. 7. Product separation on Dowex 50 column. Sample, 80 ml of 0.25 M glycine after irradiation; radiation, 35-Mev helium ions; dose 4×10^{20} ev/ml. (For a description of peaks A and B see Table II.)

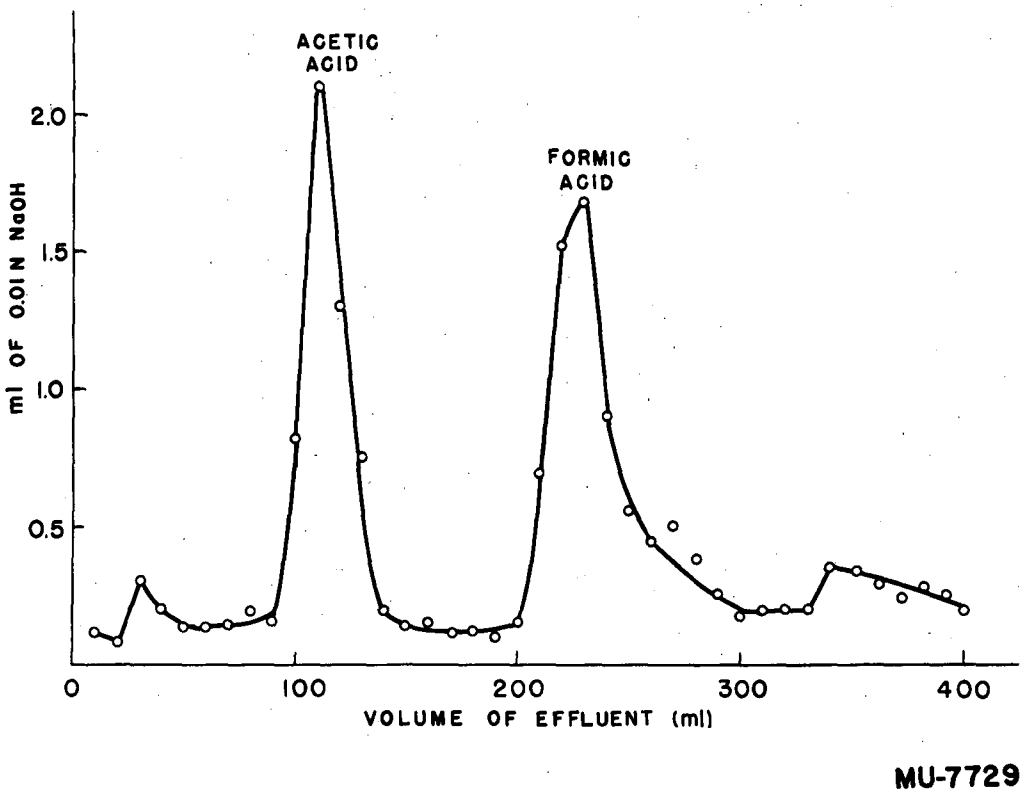

Fig. 8. Elution curve for silicic acid column where sample put on column was obtained from the water effluent of a Dowex 50 column (see Fig. 7). Target material was 0.25 M glycine given a standard dose of 4×10^{20} ev/ml.

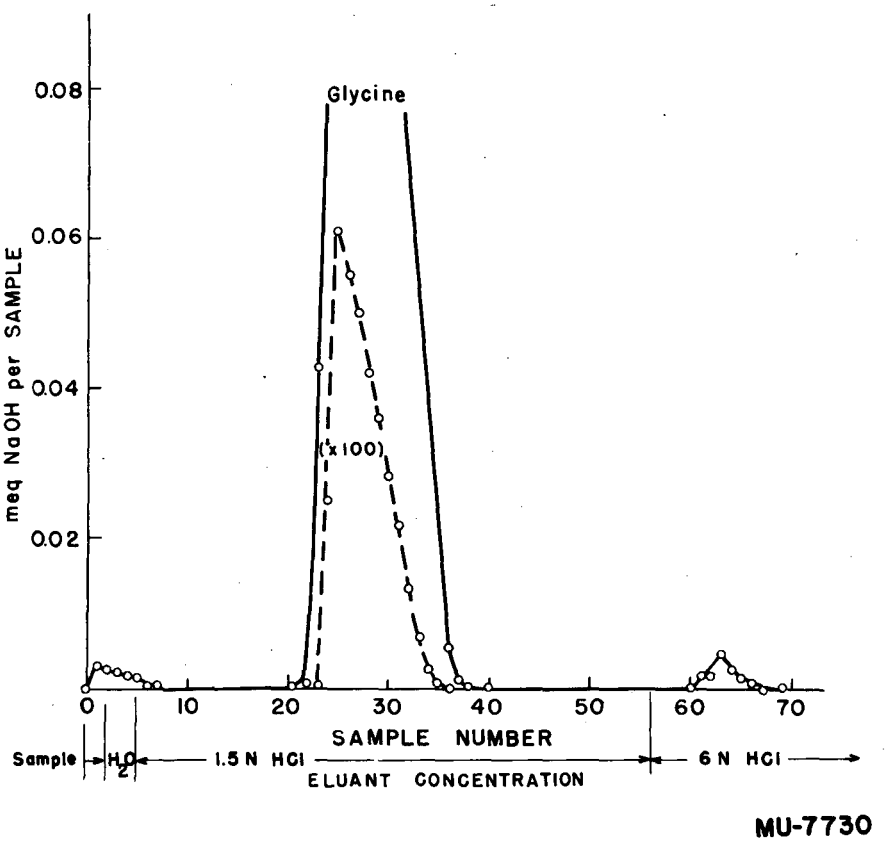

Fig. 9. Elution curve for a Dowex 50 column where the sample put on the column was a H_2O solution containing 4.75 g of unirradiated glycine. This would correspond to 250 ml of 0.25 M target solution.

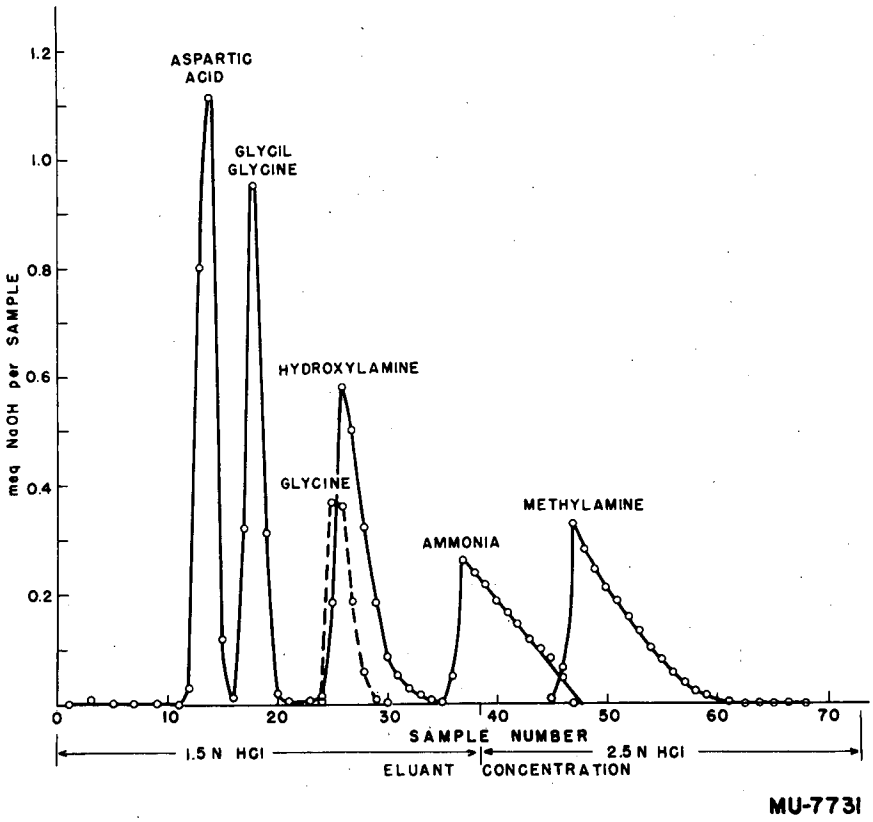

Fig. 10. Elution curve for a Dowex 50 column where the sample put on the column was a known mixture of the indicated compounds.

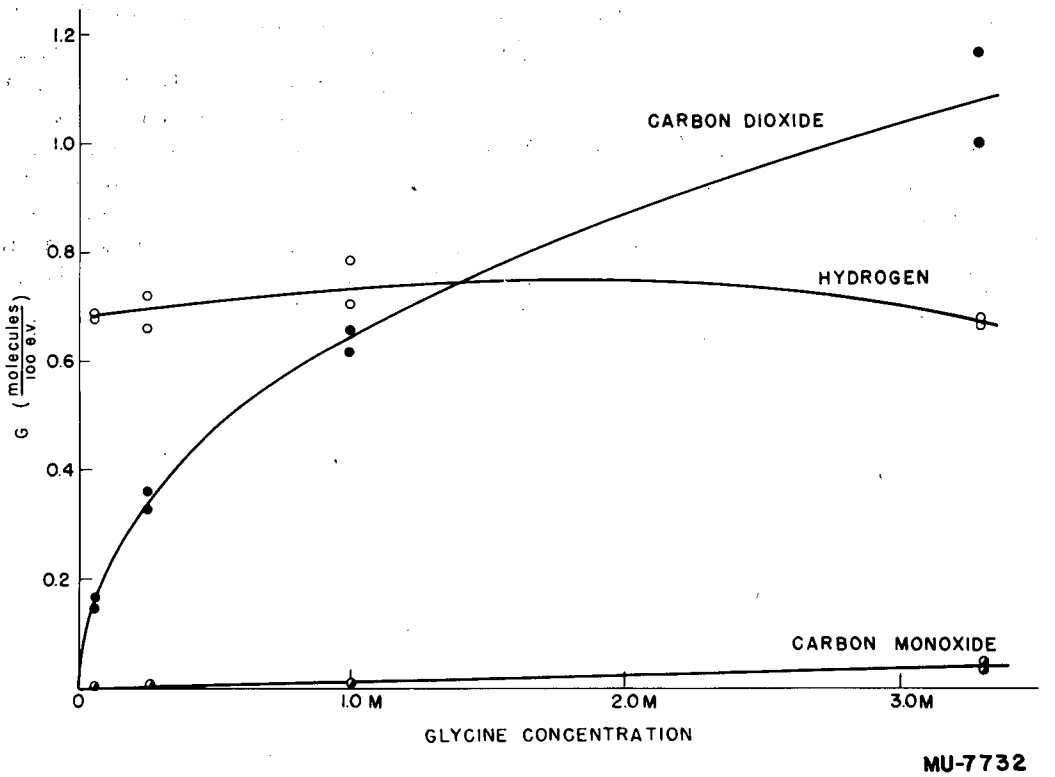

Fig. 11. Curve showing relationship of H_2, CO, and CO_2 yields to glycine concentration where the dose is held constant at 1×10^{20} ev/ml.

BIOLOGICAL STUDIES OF RADIATION EFFECTS

John H. Lawrence, M.D., in charge

VARIATION OF RADIOSENSITIVITY AND RELATIVE BIOLOGICAL EFFECTIVENESS IN HAPLOID YEAST*

Mortimer M. Elkind† and Carl A. Beam

The radiosensitivity of haploid Saccharomyces cerevisiae, SC-7, has been studied in the region of exponential survival, using 50-kv x-rays and Po^{210} alpha particles (3.2 Mev). The x-ray source had a full-wave rectified supply and 1.0 mm beryllium inherent filtration. The alpha source consisted of 3.1 mc of electrodeposited Po^{210} 3/16-inch in diameter. The dose rate ratio alpha to x-rays was about 0.8. Cultures were grown on YED agar (1/2% Difco yeast extract 1% dextrose) for 18 hours at 30° C. These cells were used as an inoculum for a YED liquid growth medium at 30° C. Log phase cells from this medium were harvested, washed, and used either in survival studies or as an inoculum for a starvation medium (5% dextrose in M/20 KH_2PO_4). Survival studies (visible colony formation) with fresh cells and cells starved up to nine days showed a change in x-ray LD_{50} (50% survival) from about 1.5 krep to 3.7 krep respectively and in alpha LD_{50} from about 2.6 krep to 1.9 krep respectively. Alpha rays are less effective than x-rays in killing fresh cells, while the reverse is true for starved cells.

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* Abstract of report presented for Radiation Research Society, May 1954.

† From the Laboratory of Biophysics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; on temporary assignment to the Donner Laboratory.

LIPOPROTEIN STUDIES

John H. Lawrence, M. D., in charge

ULTRACENTRIFUGAL STUDIES OF THE HIGH-DENSITY SERUM LIPOPROTEINS IN CLINICALLY HEALTHY ADULTS

Oliver F. deLalla, Harold A. Elliott, and John W. Gofman

Introduction

Lindgren and co-workers[1] have described the properties and methodology for the ultracentrifugal study of the entire spectrum of lipoproteins present in human serum. The three most dense lipoproteins described by Lindgren et al. represent the subject of present considerations. These lipoproteins have been identified by their estimated hydrated densities as a lipoprotein of density 1.05 g/ml, a lipoprotein of density 1.075 g/ml, and a lipoprotein of 1.145 g/ml. At present the precise interrelationship of the chemically isolated alpha lipoproteins described by Oncley et al.[2] to these three ultracentrifugally defined high-density lipoproteins is not completely clear. Since the exact relationship to chemically isolated alpha lipoproteins remains indeterminate, we have avoided the designation of the three high-density lipoproteins as alpha lipoproteins and instead have utilized the following nomenclature;

The lipoprotein of hydrated density 1.05 g/ml = HDL_1*
The lipoprotein of hydrated density 1.075 g/ml = HDL_2
The lipoprotein of hydrated density 1.145 g/ml = HDL_3

The role of the low-density lipoproteins (of hydrated density less than 1.04 g/ml) in the systematics of serum lipid transport have been described [3, 4, 5]. Ultimate further understanding of lipid transport requires similar knowledge of the population distributions of the three high-density lipoproteins and of their interrelationships with the low-density group of lipoproteins. The high-density lipoprotein determinations described below were made on 566 randomly chosen clinically healthy adults of both sexes, between the ages of eighteen and sixty-nine years of age.

Materials and Methods

The procedure of Lindgren et al. involving preparative and analytic ultracentrifugation is in a sodium chloride – D_2O – H_2O system of

* The designation HDL is used to indicate the high-density lipoproteins for contrast with the low-density group of lipoproteins, for which the component of highest hydrated density is 1.04 g/ml. The cutoff at 1.04 g/ml is arbitrary. Reference to HDL_1, HDL_2, or HDL_3 lipoprotein does not infer that a single discrete lipoprotein at each density is necessarily involved. The homogeneity or lack thereof of such lipoproteins deserves further investigation.

solvent density equal to 1.24 g/ml. All three high-density lipoproteins were observable in the analytical ultracentrifugation at a density of 1.24 g/ml. This analytical method allowed the quantitative determination of the sum of the concentrations of the HDL_2 plus HDL_3, but was unsatisfactory for the complete resolution of the HDL_2 from HDL_3 so that their individual concentrations could be measured. For this reason an additional ultracentrifugal procedure at a density of 1.125 g/ml was designed for the separate measure of the concentration of the HDL_2. The detailed description of the preparative and analytical ultracentrifugal procedures, including film analysis, employed for the determination of the three high-density lipoproteins is described by deLalla and Gofman[6].

The clinically healthy subjects for this study were obtained from two sources. Males and females below the age of 30 years were volunteers from the student population of the University of California at Berkeley. All other subjects, above the age of 30 years, were randomly selected from the population under study by the Heart Epidemiology Study Group at Framingham, Massachusetts. All subjects had had a recent complete medical examination. The subjects included in the present study as clinically healthy individuals represented those meeting certain requirements in their medical examination. All individuals included in the study had blood pressures, at examination, below 140 mm Hg systolic and 90 mm Hg diastolic. The following illnesses recorded in the medical history or discovered during examination were sufficient to exclude individuals from this study: diabetes, nephritis, rheumatic fever, rheumatoid arthritis, syphilis, tuberculosis, peptic ulcer, asthma, hepatitis, cardiovascular disease, cancer, epilepsy, hyper- or hypothyroidism, adrenal disease, Raynaud's disease, or pernicious anemia.

A laboratory finding of an abnormal electrocardiogram, abnormal chest roentgenogram, anemia, albuminuria, or glycosuria was considered sufficient to exclude a subject from this study. It is evident that if any of these abnormalities or disease states were not overt to the examiner, the subject would be included in the study. Thus the subjects included are to be regarded as clinically healthy within the limits of the criteria described. The total number of subjects who qualified with these criteria were 566 in all, 229 of whom were males, and 337 females. The analysis of all three high-density lipoproteins was made for all these subjects, segregating the population studied by sex and into the following age groups: 18–19, 20–29, 30–39, 40–49, 50–59, and 60–69 years.

Results

(a) The HDL_1: The mean serum concentrations of the HDL_1, the standard deviations of the distribution, and the standard errors of the means are presented in Table I.

(b) The HDL_2: The mean serum concentrations of the HDL_2, the standard deviations of the distribution, and the standard errors of the means are presented in Table II.

(c) The HDL_3: The mean serum concentrations of the HDL_3, the standard deviations of the distribution, and the standard errors of the means are presented in Table III.

(d) The Intercorrelations of the High-Density Lipoproteins: In Tables IV, V, and VI are given the calculated Pearson product-moment correlation coefficient between the HDL_1 vs HDL_2, HDL_1 vs HDL_3, and HDL_2 vs HDL_3, respectively, for both sexes and for the several age categories.

Discussion

The HDL_1: (see Table I) Inspection of the mean HDL_1 levels in either sex reveals no large trends of lipoprotein concentrations with age. Application of the t-test demonstrates that the recorded differences in mean levels with age fail to show significance at the 1% level. However, the t-test does reveal that, for the age group under 40 years the mean level of HDL_1 appears to be significantly lower in the female than in the male (1% level of significance). It is not possible from these data to demonstrate any significant sex difference in HDL_1 level beyond the age of 40 years.

The HDL_2: (see Table II) One feature is outstanding in the results of the measurement of the HDL_2, namely the large difference between the male and female sex for the age range from 20 years to 60 years. For each decade in this range the mean HDL_2 level is much higher in the female than in the male. For the 18–19 year age group the same trend appears to be maintained, although the difference can be proven significant only between the 1% and 5% level from these data. Above the age of 60 years no significant male-female difference can be demonstrated within the limited data now available. In the male sex there is a fall in HDL_2 concentration in the 20–29-year age group as compared with the 18–19-year age group that is significant at the 1% level. In the range from 20 years to 60 years there is no further significant change in HDL_2 concentration in males with age. There is an apparent rise in HDL_2 concentration in the 60–69-year-old male compared with the 50–59-year age group, signicant between the 1% and 5% level. It is evident that a larger series of males beyond 60 years of age is required to determine more conclusively whether this rise is real. In the female sex no significant difference in mean HDL_2 concentration can be demonstrated for 18–19-year-olds as compared with 20–29-year-old females. However, a decrease, significant at the 1% level, in the mean HDL_2 concentration is observed in the 30–39-year-old females as compared with the 20–29-year-old females. It must be noted, however, that the age of 30 years represents the dividing line between the younger group of females collected in Berkeley, California, and the older age groups collected in Framingham, Massachusetts. Therefore, we cannot rule out the possibility that the observed significant difference in HDL_2 level in the 20–29-year-old females as compared with the 30–39-year-old females is due to a factor in some way geographically determined. On the other hand the observed difference may very well reflect a metabolic alteration with age in the female, independent of geographical considerations. In any event the observed differences between 18–19-year-old males as compared with 20–29-year-old males cannot be geographically determined, since both groups of subjects were of the Berkeley sampling. Beyond the age of 30 years in the female no significant alterations in HDL_2 concentrations with age are demonstrable.

If the assumption is made that the possible geographic factor alluded to above is unimportant, then it appears that, within the age spans studied,

Table I

The HDL_1 Concentration in Males and Females as a Function of Chronological Age.

Age group	No. of subjects	Mean HDL_1	Standard deviation of the distribution	Standard error of the mean
years		mg%	mg%	mg%
Males				
18–19	15	21.8	3.6	1.0
20–29	28	21.6	7.7	1.5
30–39	82	17.2	7.9	0.9
40–49	54	18.4	10.5	1.4
50–59	39	18.8	8.3	1.4
60–69	11	23.5	7.8	2.5
(Total subjects)	229			
Females				
18–19	22	17.6	6.2	1.4
20–29	28	15.8	5.8	1.1
30–39	132	14.3	6.5	0.6
40–49	104	15.9	6.1	0.6
50–59	44	16.3	5.9	0.9
60–69	7	16.6	12.7	5.2
(Total subjects)	337			

Table II

The HDL_2 Concentration in Males and Females as a Function of Chronological Age

Age group	No. of subjects	Mean HDL_2	Standard deviation of the distribution	Standard error of the mean
years		mg%	mg%	mg%
Males				
18-19	15	82.5	18.7	5.0
20-29	28	59.6	26.0	5.0
30-39	82	57.7	34.9	3.9
40-49	54	60.3	32.0	4.4
50-59	39	64.8	30.9	5.0
60-69	11	95.8	39.8	12.6
(Total subjects)	229			
Females				
18-19	22	109.8	45.2	9.9
20-29	28	141.3	64.0	12.3
30-39	132	102.2	42.4	3.7
40-49	104	101.6	39.4	3.9
50-59	44	117.1	50.9	7.7
60-69	7	93.4	40.6	16.6
(Total subjects)	337			

the female shows a drop in mean HDL_2 level from the peak value apparently ten years later than the male.

The HDL_3: (see Table III) In the 18–19-year age group no significant difference between males and females in the mean HDL_3 level can be demonstrated. However, for the age span 20–60 years, in each decade it can be demonstrated the mean HDL_3 level in females is higher, at the 1% level of significance, than in the corresponding males.

In the age span from 18–29 years, for either sex alone, no significant change in mean HDL_3 level as a function of age can be demonstrated. For both sexes, however, there appears to be a drop in mean HDL_3 level in the 30–39-year age group as compared with the 20–29-year age group, the significance being at the 1% level in the female and between the 1% and 2% level in the male. Again, as was mentioned for the HDL_2 data, the factor of possible geographic influence cannot be overlooked for differences which become manifest at the dividing line of 30 years of age.

In the males no significant age trends can be demonstrated beyond 30 years of age. In the female, however, there appears to be some increase in mean HDL_3 level in the 50–59-year age group as compared with the 30–39-year age group. This apparent increase, however, must be regarded only as borderline, since it is at the 5% level of significance.

It is of interest that while the female in general has been shown above to be higher than the corresponding male in both the HDL_2 and HDL_3 levels, the magnitude of the sex difference is approximately 2 to 2.5 times as great in the HDL_2 levels as in the HDL_3 levels, when considered on a standard score basis*[7].

Some data exist in the literature on the subject of so-called "alpha" lipoprotein as measured by chemical fraction (Russ et al.[8]) and ultracentrifugally by Lewis and Page[9]. The work of Russ, Eder, and Barr provides data for the cholesterol recovered in Fraction A of the Cohn fractionation method 10.[10] These authors state that the "α_1-lipoprotein" is to be found in Fraction A. However, they make no comment concerning the possible presence of several components in this fraction, nor do they give the percentage that the cholesterol represents of the total lipoprotein. As a result it is impossible to compare their findings of the quantity of cholesterol, in whatever form it is present in Fraction A, with our results on the individual HDL_1, HDL_2, and HDL_3. Further, their limited data on 20 subjects over the age span 18–35 years for females and 24 subjects over the 18–35 year span for males would have completely obscured the changes observed in the present work within this age span, even if they were measuring the HDL_2 and HDL_3 components combined. Lewis and Page have utilized the method of Lindgren et al.[1] for ultracentrifugal study of the lipoproteins in a medium of density 1.21, except for the minor modification of substituting KBr for NaCl and D_2O in achieving the density 1.21 g/ml they used. As was pointed out earlier in this discussion (see section on Materials and Methods)

*Comparisons on a standard score basis refer to differences in mean as related to the standard deviation of the distribution.

Table III

The HDL_3 Concentration in Males and Females as a Function of Chronological Age.

Age group	No. of subjects	Mean HDL_3	Standard deviation of the distribution	Standard error of the mean
years		mg%	mg%	mg%
Males				
18–19	15	203.0	32.5	8.7
20–29	27*	195.5	36.7	7.2
30–39	82	173.3	49.2	5.5
40–49	54	176.7	43.0	5.9
50–59	39	181.1	53.7	8.7
60–69	11	184.0	38.4	12.1
(Total subjects)	228			
Females				
18–19	22	204.5	30.7	6.7
20–29	28	222.6	37.1	7.1
30–39	132	191.9	44.6	3.9
40–49	104	198.6	39.3	3.9
50–59	43*	207.1	30.8	4.8
60–69	7	200.3	39.5	16.1
(Total subjects)	336			

*In the two groups designated one case had analyses for the HDL_1 and HDL_2 but did not have the HDL_3 analysis because of insufficient quantity of serum available.

this type of run is unsatisfactory for the resolution of the HDL_2 and HDL_3. It appears further that Lewis and Page failed to utilize the length of time of centrifugation described in the Lindgren et al. paper, and that at least for the HDL_3, which is the most abundant high-density lipoprotein, their analyses could not possibly have been quantitative under the conditions they describe. Direct evidence that their results may not be quantitative may be found by comparing the analyses reported by Lewis and Page for what they call α_1 -lipoprotein. If the 1.21 g/ml run were used correctly according to the Lindgren et al. procedure, they should have been able to measure the sum of HDL_2 and HDL_3 combined. From their data for so-called - S = 4 lipoprotein (their "α_1 -lipoprotein") for males 18-34 years; α_1 lipoprotein = 153.7 mg%. From Table II and Table III, by combining our means for this age range for males, the combined HDL_2 and HDL_3 value would be 260 mg%. Thus the Lewis and Page value is about 40% low. Similarly, for females, our combined HDL_2 and HDL_3 would be 315 mg%. The Lewis and Page value for "α_1-lipoprotein" is 183 mg %, which is again approximately 40% low. It appears likely that the incomplete separation due to inadequate centrifugation is the basis for their seriously discrepant results. This renders any comparison of the results herein reported with those of Lewis and Page essentially without value. The values reported by Lewis and Page for "α_2 lipoprotein" are of the order of magnitude of those found by us for the HDL_1. Their values, however, are approximately 1/2 to 2/3 of our values for HDL_1.

Intercorrelations of the High-Density Lipoproteins

It is of interest biologically to know to what extent the factors involved in the control of the serum levels of the three high-density lipoproteins are alike and to what extent they differ. One approach to an evaluation of this is the use of the Pearson product-moment correlation between the levels of any pair of lipoproteins. Such correlations are evaluated in Tables IV, V, and VI. It is evident from Table IV and Table V that no strong intercorrelations exist between the HDL_1 and either the HDL_2 or HDL_3. For most of the age decades involved and for both sexes it is impossible even to demonstrate any correlation of significance. However, in 3 of the 12 groups there does appear to be a significant negative correlation between the HDL_1 and HDL_2. It appears therefore that even though there may exist a negative correlation between these two lipoproteins, it is probably of very low order. For most of the groups no significant correlation can be demonstrated between the HDL_1 and HDL_3 lipoproteins, although in 3 groups a significant positive correlation is noted. Again it appears, therefore, that if the HDL_1 and HDL_3 are positively correlated, the interrelationship is of a low order.

For 8 of the 12 groups considered no significant correlation is demonstrable between the levels of HDL_2 and HDL_3. In three groups a low positive correlation of borderline significance was found, and in one group a low positive correlation, significant at the 1% level, was demonstrated. Therefore, an over-all relationship of HDL_2 and HDL_3 levels, if positive, is of low order.

Consideration of all these intercorrelation studies indicates that the metabolic factors involved in the regulation of the serum level of any one

Table IV

The Pearson Product-Moment Correlations between the HDL_1 and HDL_2

Age group years	Number of Cases	Pearson r	Test of Significance of r's being different from zero.*
Males			
18–19	15	-0.19	Not significant
20–29	28	-0.39	Significant at the 5% level
30–39	82	+0.03	Not significant
40–49	54	-0.20	Not significant
50–59	39	-0.14	Not significant
60–69	11	+0.35	Not significant
(Total subjects)	229		
Females			
18–19	22	-0.49	Significant between 1% and 5% levels
20–29	28	-0.34	Not significant
30–39	132	-0.11	Not significant
40–49	104	-0.28	Significant at the 1% level
50–59	44	-0.27	Not significant
60–69	7	+0.48	Not significant
(Total subjects)	337		

* In Tables IV, V, and VI significance of calculated Pearson r values assessed by reference to Table D in Appendix of "Fundamental Statistics in Psychology and Education" by Guilford.

Table V

The Pearson Product-Moment Correlation Between the HDL_1 and the HDL_3

Age group years	No. of cases	Pearson r	Test of significance of r's being different from zero.*
Males			
18–19	15	+0.18	Not significant
20–29	27	-0.33	Not significant
30–39	82	+0.29	Significant at the 1% level
40–49	54	-0.07	Not significant
50–59	39	+0.34	Significant at the 5% level
60–69	11	0.0	Not significant
(Total subjects)	228		
Females			
18–19	22	-0.24	Not significant
20–29	28	+0.44	Significant between the 1% and 5% levels
30–39	132	-0.04	Not significant
40–49	104	+0.04	Not significant
50–59	43	0.00	Not significant
60–69	7	-0.11	Not significant
(Total subjects)	336		

* In Tables IV, V, and VI significance of calculated Pearson r values assessed by reference to Table D in Appendix of "Fundamental Statistics in Psychology and Education", by Guilford.

Table VI

The Pearson Product-Moment Correlations Between the HDL_2 and HDL_3

Age group years	No. of Cases	Pearson r	Test of Significance of r's being different from zero.*
Males			
18–19	15	-0.23	Not significant
20–29	27	+0.21	Not significant
30–39	82	+0.38	Significant at the 1% level
40–49	54	+0.17	Not significant
50–59	39	+0.22	Not significant
60–69	11	+0.17	Not significant
(Total subjects)	228		
Females			
18–19	22	+0.43	Significant at the 5% level
20–29	28	-0.16	Not significant
30–39	132	+0.17	Significant at the 5% level
40–49	104	-0.09	Not significant
50–59	43	+0.34	Significant at the 5% level
60–69	7	-0.26	Not significant
(Total subjects)	336		

* In Tables IV, V, and VI significance of calculated Pearson r values assessed by reference to Table D in Appendix of "Fundamental Statistics in Psychology and Education", by Guilford.

of the high-density lipoproteins are largely independent of those involved in the regulation of the level of either of the other high-density lipoproteins.

Summary

1. Measurements of three high-density lipoproteins in the serum of 566 clinically healthy adults have been made.

2. Analysis of the age and sex trends in mean high-density lipoprotein levels for the age span 18-69 years has been made.

3. Possible interrelationships in the serum levels of the three high-density lipoproteins were evaluated.

Acknowledgment

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HEALTH CHEMISTRY

Nelson B. Garden

PROGRESS REPORT

Equipment Development Group

The Equipment Development group (having successfully set up and operated several experiments as well as a semiproduction operation involving multicurie quantities of alpha, beta, and gamma emitters) is now redesigning whatever features seemed to offer opportunities for improvement.

More extensive use of plastic enclosures can be undertaken since a radiofrequency welder has been made which produces a quick, reliable weld up to twelve inches in diameter.

Airborne Activity Control Group

This group engaged in the following consultations: (1) the ventilation aspects of the proposed decontamination building at Livermore were planned and submitted to the Plant Engineering group; (2) samples of all plastic hood canopy and plastic-coated duct work for Bldg. 70 were examined and approved; (3) plans for the conversion of Bldg. 4 were discussed and submitted; (4) plans for a forthcoming Livermore project were formulated, based on the work performed last quarter in Bldg. 106, Livermore.

An electrically actuated manometer switch has been developed by a member of this group to replace the mechanically operated switch previously employed in box exhaust manifolds. The new device serves to trigger a standby exhauster in case of blower failure as well as to indicate the static suction in the manifold. Field trials are under way; laboratory trials have been successful.

Two new experimental scrubbers have been designed and fabricated with design simplicity and space economy at good flow rates as the criteria. Efficiency trials will follow.

A year's experience has been accumulated on the use of the so-called graded filter (B fiber-PF 105-CWS 6 in one housing) as a replacement for the two-unit PF 105 plus CWS 6 assemblies. The experience has shown the economy and desirability of the singly-housed assembly.

The improvement of a qualitative air-flow indicator mounted in transparent ducting has been effected by replacing the swinging vane by one mounted on a single Saran fiber to eliminate all bearings and metals and most of the fabrication time.

Activity Handling Group

Two new containers for the transportation of radioactive material were designed during this period -- one for the hauling of a highly active

irradiation from Idaho Falls by UCRL truck and another designed to dissipate thermal heat generated by its contents.

A survey and codification, for ease of use, of the existing national regulations regarding transportation of radioactive materials by rail, air, truck, etc., is being prepared.

Monitoring Group

A new beta-gamma meter, developed by the Electronics Department, is being used successfully by the Monitoring group in place of the Zeus meter. Its range is from 20 mr/hr to 200 r/hr.

Considerable experience in tritium monitoring is being afforded to members of this group.

General

The yearly audit of the accountability and handling methods of Source and Fissionable materials at Berkeley was completed by a team from the Atomic Energy Commission; the findings were held satisfactory by the auditors.

HEALTH PHYSICS

Burton J. Moyer

STATISTICAL SUMMARY OF MONITORING PROGRAM

Survey Instruments Maintained

1.	B-γ Ionization Chamber	62
2.	I. D. L. Portable Survey Instruments	20
3.	Cutie Pies	3
4.	Recording γ-Intensity Meters	22
5.	Victoreen Proteximeter	3
6.	Fast-Neutron Proportional Counters	8
7.	Slow-Neutron Proportional Counters	15
8.	Fast-Neutron Proportional Counter (Portable)	11
9.	Slow-Neutron Portable Unit	4
10.	Balanced Chamber - Fast Neutron - Portable	3
11.	Special Tissue Wall Survey Instrument	1

Personnel Meters in Use

1.	Total Personnel Covered with Film Badges	2, 923
2.	Total Man Days Coverage with Pocket Chamber	6, 082
3.	Total Man Days Coverage with Pocket Dosimeters	6, 082
4.	Total Man Days Coverage with Pocket Chambers (S. N.)	4, 731

Cases of Weekly Exposure Above .3r

Weekly Film Expos. above	184" Area	60" Area	Lin. Acc.	Chem.	Other	Total
0.3	1	21	3	64	4	93
0.5	0	7	2	28	0	37
1.0	0	1	0	8	0	9
1.5	0	0	0	4	0	4
2.0	0	0	0	3	0	3
2.5	0	0	0	3	0	3
5.0	0	0	0	0	0	0

Information Division
6-3-54 am