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REPORT OF HEALTH DIVISION

for

MONTH OF APRIL 1945

DECLASSIFIED Per Letter Instructions Of TID-1003
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Report Received: April 26, 1945 Figures Received: May 4, 1945
Issued: MAY 9 1945

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A B S T R A C T S

CLINICAL MEDICINE AND MEDICAL RESEARCH

During the month of March 16 to April 15, 1945, 200 physical examinations were done; 25 were academic and 175 were non-academic personnel. 71 pre-employment physical examinations were done; 5 persons were rejected because of findings on clinical or laboratory examinations. During this same period 4550 clinical laboratory examinations were made. This included laboratory work on 60 new personnel, 248 controls, and 644 in the work hazard group. Abnormalities considered on the basis of the white blood count alone showed individuals with abnormalities in these groups of 14, 74, and 147 respectively.

T in aqueous solutions at pH values above 6 behaves as an anion and does not pass cellophane membranes on ultrafiltration. Passage occurs when an electric current is applied as in electrodialysis experiments. Electrodialysis of T is proof that T is not found in ultrafiltrates because of its electronegative charge. T in protein solutions does not pass cellophane membranes because it has combined with the protein molecule; as a consequence T does not pass the membrane on electrodialysis. T is excreted in the urine because of ultrafiltration of the T-bicarbonate complex. Evidence for the suggestion is given in experiments on ultrafiltration of T in the presence of bicarbonate and in the presence of dialyzed plasma plus bicarbonate.

Low coproporphyrin values have been found in the urines of dogs treated with product and total body x-ray. A green pigment (probably biliverdin) has been found in these dogs one to two weeks after radiation administration. Studies of T fluoresence in sodium fluoride have been completed indicating that the quenching problem can be solved by either suitable dilution or by suitable correction factors.

BIOLOGICAL RESEARCH SECTION

The condensed spark has been tested as a method of producing aerosols. It has the advantages of the arc of smaller particle size, no carbon monoxide problem, and low temperature which may make possible aerosolization of molecules other than oxide. As yet, however, the reproducibility and yields have run lower than with the arc.

We have previously exposed rats to a vapor of carrier-free 330 day RuO_4. In order to determine the effect of valence state on absorption from the lungs a group of rats was exposed to an aerosol of Ru which was probably in the +3 or +4 valence state. Analyses are as yet incomplete but indicate a much lower initial absorption rate for the aerosol as compared to the RuO_4 vapor.

Sheets of proliferative septal cells in the lungs of rats sacrificed 68 days after inhalation of radio-cerium were distinctly abnormal in appearance and configuration but showed no definite evidence of neoplasia.

Splenectomized mice treated with Sr^{89} became anemic whereas in unoperated mice Sr^{89} causes a leucopenia but no anemia.

In 3 week chicks at early intervals following 100r of X-radiation there was slight damage to bone marrow, spleen, thymus and nerve sheath cells only. All these tissues had returned to normal by 48 hours with the exception of the bone marrow which showed depletion of hematopoiesis of questionable significance as late as 12 days, but not at 17 days.

Many small lymphocytes in the rabbit appendix, spleen, lymph node and thymus were destroyed by 50r of X-radiation; the damage was greatest in the appendix and less in the other organs, in the order named.

A dog which received total body x-radiation of 50r daily survived 18 days after the beginning of treatment. It showed a rapid decline in weight, food and water consumption, in white blood cell count and a slow decline in red blood cell count. Total pigment excretion was diminished. Terminally heart rate and rectal temperature were elevated. At autopsy the dog resembled animals which die after a single dose of x-radiation.

A single dose 10r x-radiation does not affect the peripheral blood of mice.

MEDICAL AND INDUSTRIAL HAZARDS SECTION

Acquisition of new high radiation level monitoring devices have shown that the skin exposure hazard in room 172, Site B Annex, is much more serious than earlier, more sensitive instruments had indicated. Remote control handling of active solutions is being developed. 4670 pocket meter readings were made during the month. 0.43% were greater than 100 mr. 2200 films were handled. Three readings were greater than 0.6 r for one week. The decontamination squad has completed its work in the service building. Decontamination of off-project University areas has begun.

RADIATION LABORATORY

A large number of pea plants were harvested that had been grown in W top-soil containing from 0.1 to 0.2 micro-curies per gram of Sr, Y, Zr plus Cb, and Ce. The most significant observation is that marked destruction of the roots took place, presumably from radiation effects. Plant studies with carrier-free radio-Tellurium show this material to be selectively deposited in the roots to a very high degree. Radio-Tellurium is absorbed very effectively by clay and in this respect resembles the corresponding behavior of the alkaline earths, rare earths, Zirconium and Columbium. An investigation of the blocking action of inert Iodine in reducing

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the uptake of I^{131} by the thyroid gland has been started. A single dose of 100 mgms. of inert Iodine reduces the uptake of I^{131}, when both Iodine isotopes are given simultaneously, to from 0.2% to 0.3% of the administered amount of radio-Iodine.

UNIVERSITY OF CALIFORNIA

Five patients received from 280 to 300 r of x-ray to the total body at 1000 K.V.; 20 r per day was given. No clinical signs or symptons developed but definite hematological alterations occurred.

NATIONAL CANCER INSTITUTE

LAF1 mice of original experiment. Total doses at present: (4.4 r, 2.2 r, 1.1 r, and 0.11 r per 8 hours per day) 3350 r, 1675 r, 840 r, and 88 r. The blood picture of the surviving animals is comparable to that of the controls with the exception of the 4 surviving animals of the 4.4 r per 8 hours level in which the red count is somewhat lowered. Incidence in malignant lymphoma is now increasing in the lower levels (1.1 r, and 0.11 r) and in the controls. New cases of malignant lymphoma have not been seen on the 2.2 r and 4.4 r levels. This seems to indicate that radiation merely decreases the latent period of spontaneous malignant lymphoma in mice, the decrease in latent period being a function of the total dose. Ovarian tumors are now observed in all mice that come to autopsy with the exception of the controls and those exposed to 0.11 r per 8 hours per day.

Strain A mice experiment. The examination of the histologic sections of lung tumors observed grossly confirm the gross findings of reported last month. For the average age of 11 months the lung tumor incidence in the control animals is approximately 50% while it rises in the experimental animals (total dose of 2500 r on the 8.8 r per 8 hours level) to approximately 75%. In any attempt to transpose these results to the situation in man one must bear in mind that strain A mice are extremely susceptible to spontaneous pulmonary tumors as contrasted to the low susceptibility of man.

Hybrid guinea pigs of original experiment. Total doses are the same as for mice of the original experiment. With the exception of the animals exposed to 4.4 r, and 2.2 r per 8 hours per day, the blood picture of controls and experimental animals is the same. Some of the animals of the 2.2 r per 8 hours level show lowered counts, while in the animals of the 4.4 r per 8 hours level all counts are lowered, especially the platelet count (26,000 to 100,000).

Rabbits. The blood picture of the controls and that of the experimental animals up to and including the [illegible].4 r per 8 hours level is essentially the same, there is however an increase in percent neutrophils with increasing total dose. In the animals of the [illegible].8 r per 8 hours level the red

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count is slightly lowered. Two animals show a decreased platelet count, in all animals the differential count is reversed.

Counts of premordial, growing and atretic follicles in serially sectioned ovaries of animals which had received doses of 880 r and 770 r on the 8.8 r per day and 8.8 r per 8 hours per day levels and 770 r on the 4.4 r per day level gave a reduction in the number of follicles present indicating that the reduction in litter size in these experiments could be due to the decrease in the number of follicles in comparison with the number of follicles of a normal ovary rather than to chromosomal changes (dominant lethal mutations).

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CLINICAL MEDICINE AND MEDICAL RESEARCH

L. O. Jacobson, Section Chief

Employees Health Service - J. Garrott Allen

March 16, 1945 to April 15, 1945

A. Total physical examinations		200
a) recheck physicals	115	
b) pre-employment physicals	71	
c) transfers	7	
d) terminal examinations	7	
e) academic	25	
f) Non Academic	175	
B. Rejected	5	
C. Routine Office Calls		806
a) first industrials	50	
b) return industrials	87	
c) blood abnormalities	9	
d) personal calls	660	
D. Refers to Billings	48	
a) industrials	7	
b) substantiating diagnosis	7	
c) personal	34	
E. Total number of visits of personnel to Drexel House		1006

Clinical Laboratory Examinations - E. K. Marks

A resume of the clinical laboratory examinations during March 16 to April 10, 1945 is as follows:

Number of Laboratory Procedures performed			Number of abnormal findings
Hemoglobins	694		114
Red counts	529		100
White counts	892	below 5000	81
		above 10000	74
Differentials	898		456
Platelets	119	below 150000	21
Urines	654		252
Retics	38		0
Wassermans	230		0
Misc.	20		0
Sedimentation rates	221		0
Hematocrits	221		0
Stippling			30
Immature cells			37

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Number of individuals examined		Number with clinical laboratory abnormalties
New Personnel	60	14 or 43%
Controls	248	74 or 33%
Work hazardous group	644	147 or 44%

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Section I L. O. Jacobson, Section Chief

On The Combination Of T With Proteins -- E. S. G. Barron

In a previous report it has been shown that T in aqueous solutions, at pH 6.5 and above, is not ultrafiltrable through the pores of a cellophane bag membrane, while at pH values below 5 it goes through readily. This peculiar behaviour of T must be due to the change of electrical charge of T; TO_2^{++} at low pH values acts as a cation while at pH values above 6 it acts as an anion. According to the double layer theory of membranes, the membrane inside (in contact with T) is negatively charged; therefore T in the anion form will be repelled and the centrifuged force used for ultrafiltration is unable to counteract the electrostatic forces. This assumption has been confirmed by electrodialysis. An aqueous solution of $TO_2(NO_3)_2$(0.001 M) was neutralized to pH 6.5 with NaOH. The solution was placed in the center compartment of an electrodialysis apparatus of the Pauli type. The electrode compartments were filled with a solution of dialyzed serum instead of a salt solution to avoid precipitation of T. An electric current was applied to the electrodes, the intenisty being of 60 mA. at the beginning of the experiment. The current fell off rapidly so that at the end of four hours it was only 10 mA. Samples were withdrawn at intervals for T analysis from the center compartment. As can be seen in Figure 1, the amount of T in the aqueous solution in the center compartment diminished by 75 per cent during the first 30 minutes. At the end of one hour, 90 per cent of the T in the center compartment had migrated through the membrane. In contrast to the ready passage of $TO_2(NO_3)_2$ through membranes under the influence of an electric current when in aqueous solutions is the lack of effect when T is in a solution of serum albumin. Here T has lost its negative charge and has become bound to the protein forming a complex compound. $TO_2(NO_3)_2$ was mixed with a solution of one per cent serum albumin and the mixture was submitted to electrodialysis under the same experimental conditions as those in the aqueous solution. At the end of one hour no T had migrated from the center compartment; it was only at the end of one and one-half hours that 10 per cent passed through the membrane. T is thus firmly bound to protein, and the failure to find T in the filtrate after ultrafiltration of dialyzed serum protein must be due partly to combination with the protein. It has also been reported that when undialyzed plasma is subjected to ultrafiltration at about pH 7.8, 50 per cent of the added T is found in the ultrafiltrate. This was attributed to combination of the excess T to plasma bicarbonate, lactate, citrate, etc. In other words, bicarbonate, lactate, citrate, etc., compete with protein for combination with T, and the fact that about 50 per cent of the added T is found in the filtrate is proof that this competition was partially successful. This is possibly the mechanism of T excretion in the urine. T bicarbonate, T lactate, T citrate, etc. must be filtered through the glomeruli leaving the T protein in the blood. As soon as organic acid complexes of T have been ultrafiltered, a new equilibrium must be established whereby T-protein dissociates to form lesser amounts of T-protein plus organic complexes of T.

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The property of aqueous solutions of T at pH values above 6 of not passing through a membrane on ultrafiltration might be utilized for the determination of the dissociation constants of T complex compounds. The total T will be equal to the ultrafiltered T complex plus the non filterable anionic T. The experiments plotted in Figure 2 give data from two kinds of complexes. In the first, (1) mixtures of neutral $TO_2(NO_3)_2$ and $NaHCO_3$ were prepared so as to give a).))1 M T solution and a definite molar ratio of $\frac{NaHCO_3}{T}$. Thus one mixture contained 0.001 M T and 0.001 M T and 0.001 M $NaHCO_3$ (ration of 1); another, 0.005 M $NaHCO_3$ and 0.001 M T (ratio of 5), etc. These mixtures were submitted to ultrafiltration and the filtrate analyzed for T. Half of the total amount of T was ultrafiltration and the filtrate analyzed for T. Half of the total amount of T was ultrafiltered at a ration of 9, i.e. when the system contained 0.009 M $NaHCO_3$ and 0.001 M T. In the second, the system contained dialyzed human plasma, $NaHCO_3$ and T. Here, half of the total amount of T was ultrafiltered at a ratio of $\frac{NaHCO_3}{T}$ of 15, i.e. 0.015 M $NaHCO_3$ and 0.001 M T. The increased ratio had to be expected as the non-filterable fraction is made up of anionic T, and T-protein. In both cases 75 per cent of T was found in the ultrafiltrate at a concentration of $NaHCO_3$ of 0.02 M to 0.03 M, the $NaHCO_3$ concentration of the blood which explains the rapid urinary excretion of T.

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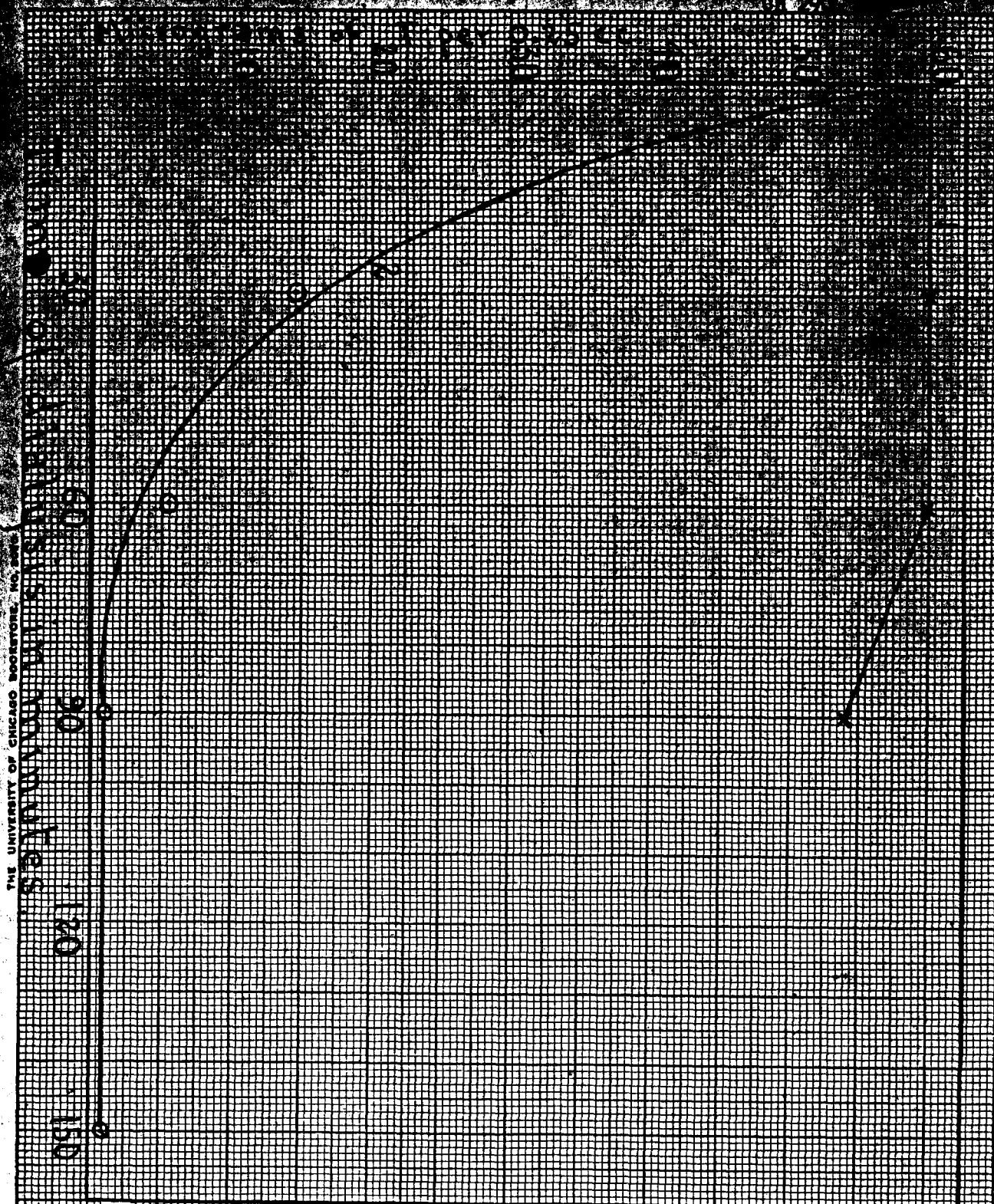

Figure I
Electrodialysis of $TO_2(NO_3)_2$ at pH 6.5

Ordinate: amount of T present in the center compartment of electrodialysis vessel (T diminishes as dialysis proceeds).
1. - 0.001 M T in 1 per cent human albumin.
2. - 0.001 M T in aqueous solution.

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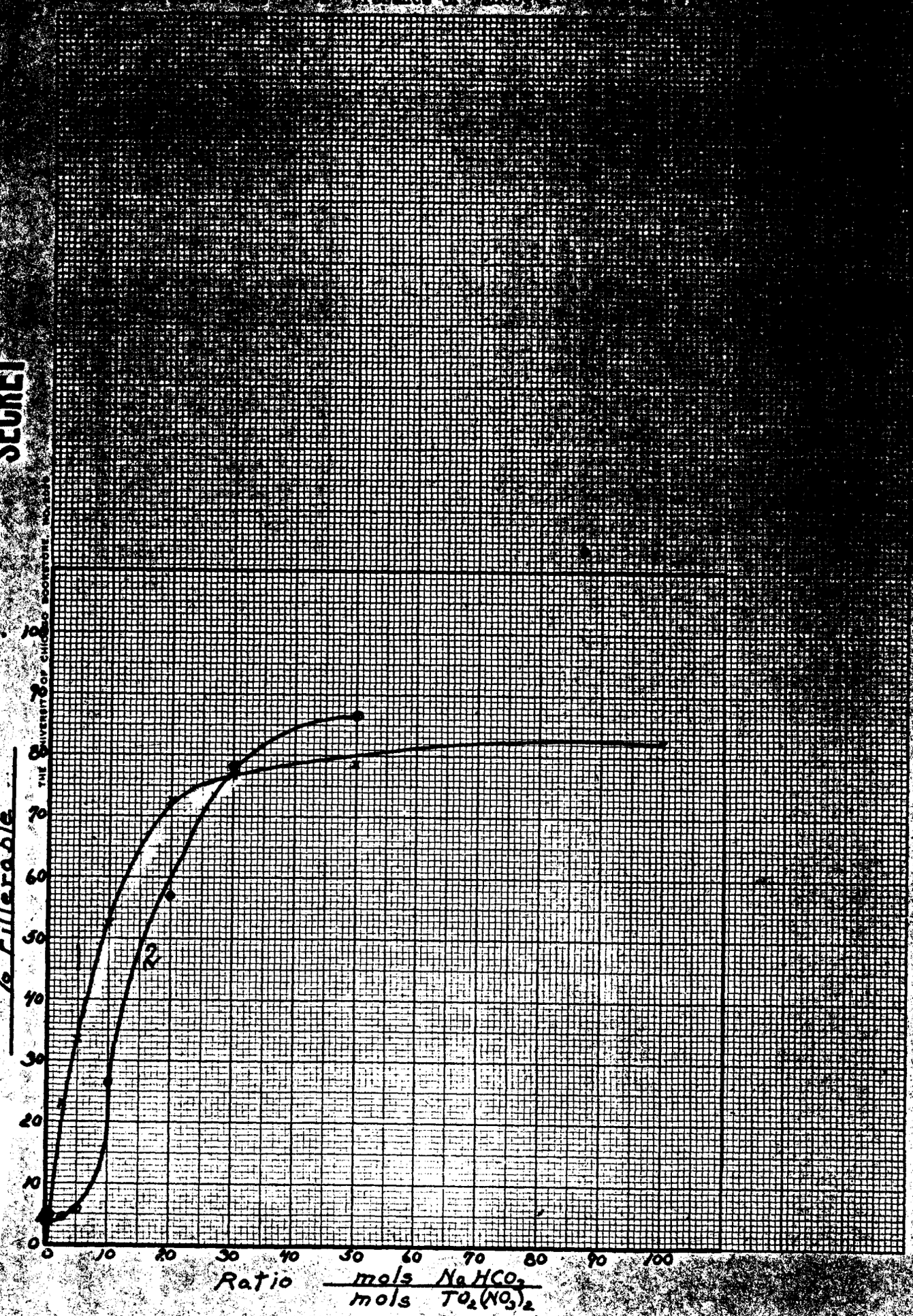
Figure II

Precipitation [illegible] in the presence of $NaHCO_3$ (1)



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I. Studies of Urinary Coproporphyrin in Irradiated Dogs

We have heretofore reported that radiation has no significant effect on the excretion of urinary coproporphyrin in irradiated rabbits or humans. Recent studies in dogs, however, lead us to modify this conclusion. In each of four dogs studied there has been a significant decrease in total coproporphyrin excretion.

Heretofore, attention has always been focused on conditions associated with elevated values such as are encountered with metal exposures. (Rise due to coproporphyrin III). Several months ago, however, we reported that a group of seven leukemia and polycythemia patients being studied exhibited uniformly low concentrations of urinary coproporphyrin. The decrease in these cases was found to be limited to the coproporphyrin I isomer; the coproporphyrin III remained essentially normal. Since such a finding is unique in the porphyrin literature we were unprepared to evaluate the reason for this change. In view of these dog studies it is of interest to note that these patients had all been receiving x-ray and/or radio-active phosphorus therapy for several months or years. Since, however, we do not have adequate control data on untreated polycythemia and leukemia patients, it is impossible to completely evaluate these findings as yet.

It should be pointed out too that coproporphyrin I excretion is increased in association with increased erythropoetic activity. It should, therefore, be reasonable to expect a diminished excretion of coproporphyrin I coincident with the diminished erythropoesis which follows radiation.

The results of the dog studies are plotted in Figures 1 through 5 in terms of the total urinary coproporphyrin excreted per day. Though in most cases determinations were done on daily samples, the data in general is plotted in terms of average values for three day periods. It might be noted that in the 23 combined control samples in the four treated and one control dog, the values ranged from 13.0 to 29.8 gamma per day. Following radiation 24 of the 50 combined samples had values of less than 13 gamma per day.

Isomer studies have not yet been done.

II. Studies of a Green Pigment in the Urine of Irradiated Dogs

The excretion of a green pigment in the urine of dogs receiving either internal or external radiation was first called to our attention by E. Painter of the Biology section. This pigment has now been noted in the urine of seven dogs receiving lethal or sub-lethal doses of x-ray

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(4 dogs) and of product (3 dogs). It has generally appeared one to two weeks after the radiation administration. It was most concentrated in the urine of the dog receiving 50r total body x-ray daily (#29) and increased steadily in amount up to the time of death. In the three animals that recovered, the excretion of this pigment was only transitory. The other two dogs were treated less than two weeks ago and are excreting the pigment at this time.

Spectropotometric analysis (Beckman) shows this pigment to have maximum absorption at 635 to 640 mu in isobutyl alcohol; acetic solution into which it is extracted from the urine. It is similar to, but has not been proven identical with biliverdin.

It might be noted that the presence of a green biliverdin-rich bile in animals has been described in association with a decrease in liver glycogen. According to E. Painter, however, a green urine is not excreted by starved dogs.

One further observation might be pertinent: The final 1% HCl extract obtained from the urine for coproporphyrin analysis in Dog #29 likewise had a blue-green color. The only similar color ever seen by the author was found several years ago in studies with C. J. Watson and I. Pass on dog and human urine following the injection of either oxyhemoglobin or crystalline hematin. The possible significance of this observation is not yet clear.

III. Studies of T fluorescence

A preliminary report has just been completed summarizing our studies to date of the microfluorometric analysis for tuballoy in a sodium fluoride flux.

In addition to analysis of some of the data reported in previous monthly reports, considerable attention is given the problem of fluorescence quenching, since its occurrence has long been one of the chief objections to the use of the method. The nature of the quenching phenomena has never been elucidated and popular opinion still subscribes to the belief that the ratio of quencher to T is the crucial factor involved.

Our own studies are based on the assumption that this is not so -- that under the conditions employed the only significant factor is the ratio of quencher to sodium fluoride. It is because of this that we are able to either eliminate the quenching factor by the use of a suitably small sample or else to correct for it by adding a known amount of T to a similar-sized sample and noting the decrease in expected fluorescence.

The pertinent data is plotted in Figures 6 through 8 below. Figure 6 demonstrates the constancy of quenching found when varying amounts of T are added to constant amounts of either urine (0.1cc) or chromium. (10 micrograms). The ordinate is plotted in terms of the ratio of the fluorescence in the quenched sample to the fluorescence of the same amount of T

[redacted]

in an unquenched sample ("quenching coefficient", Qa = 1 in the absence of quenching).

Figure 7 illustrates the variation in quenching produced by varying the amount of quencher. The result is essentially the same whether the T content also varies or remains constant.

The mixed quencher solution used contained equal amounts by weight of iron, lead, copper, calcium, magnesium, bismuth, aluminum, and chromium in nitric acid solution. Iron was similarly studied. Analyses were made of progressively diluted samples of an Fe:T solution in a ratio of 1000: 1 by weight. In addition to the above, 0.1 microgram samples of T were added to progressively diluted samples of the (T-free) quencher solution, and of thorium nitrate and chromium nitrate solutions.

In this figure 7 the axes have all been shifted horizontally to make them coincide with a theoretical curve at the point of 50% quenching. It is seen that quenching increases rapidly when quencher concentration exceeds a certain point. This point varies for different quenchers. Thus, chromium quenches appreciably at lower concentrations than do the other substances studied.

The derivation of the theoretical curve is too lengthy to be given here in full detail. Briefly, an expression[1]

$$Qa = \frac{1 - e^{-h(a_3 + a_5)}}{h(a_3 + a_5)}$$

is derived for quenching by light absorption, where Qa is the ratio of the "average" light transmission of a quenched preparation to the "average" light transmission of a pure T preparation, h is the thickness of the T-NaF phosphor, a3 is the absorption coefficient of the phosphor and a5 is the absorption coefficient for emitted fluorescent light.

From this, in order to correlate the behavior of different substances, is derived the equation

$$Qa = \frac{1 - e^{-1.59365}}{1.59365}$$

where s is a concentration coefficient, being the ratio of the amount of quencher in the preparation to the amount of quencher that gives 50% quenching. This equation was used in plotting the theoretical curve.

In Figure 8 is plotted the data on the quantitation of fluorescence of pure T, of T plus iron and of T plus mixed quencher. (Progressively diluted samples of T plus quencher were studied in all cases; therefore, the ratio of T to quencher remained constant, but the ratio of quencher to NaF varied markedly). It will be noted that the fluorescence emitted in the T plus quencher samples approaches that produced by pure T in NaF as the dilution increased. It follows, therefore, that the effect of quenching agents can be practically eliminated by the analysis of adequately small samples.

The amount of quencher necessary to yield 50% quenching is indicated by the point of intersection of the 50% quenching curve and the curve of T plus quencher.

[redacted]

It should be pointed out that the choice of analytical method and the degree of sensitivity required is governed largely by the quenching range at which one works, if one is to avoid laborious preliminary chemical purification and the use of special quenching correction techniques. Thus, for urine, quenching becomes a significant factor when more than about 0.05 cc portions are analyzed. If we require a method that is sensitive to at least 10 micrograms per liter, then it must be able to detect a total of 0.0005 micrograms in the 0.05 cc sample of urine.

It is because of this that we have endeavored to markedly increase the sensitivity of our analytical instruments.

During the past month a new photoeletric fluorophotometer, built for an associated project, has been compl ted. It is the most sensitive of the four models constructed to date. The instrument is capable of detecting fluorescence from less than 10^{-11} grams T, but high and somewhat variable sodium fluoride blanks make accurate work at this level impossible at the present time. At best we have thus far been able to work with suitable accuracy "only" down to levels of almost 10^{-10} grams.

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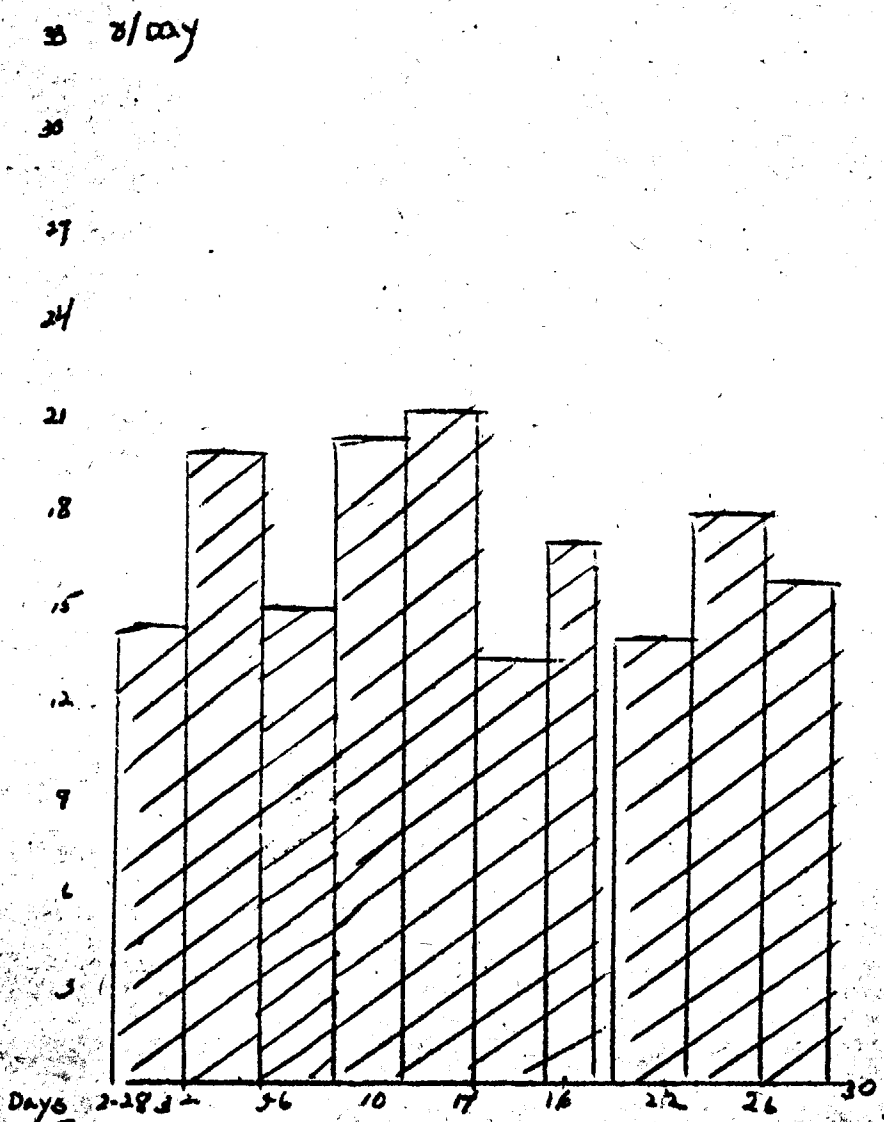

Figure 1.
Urine Coproporphyrin Excretion in Control Dog (#40)

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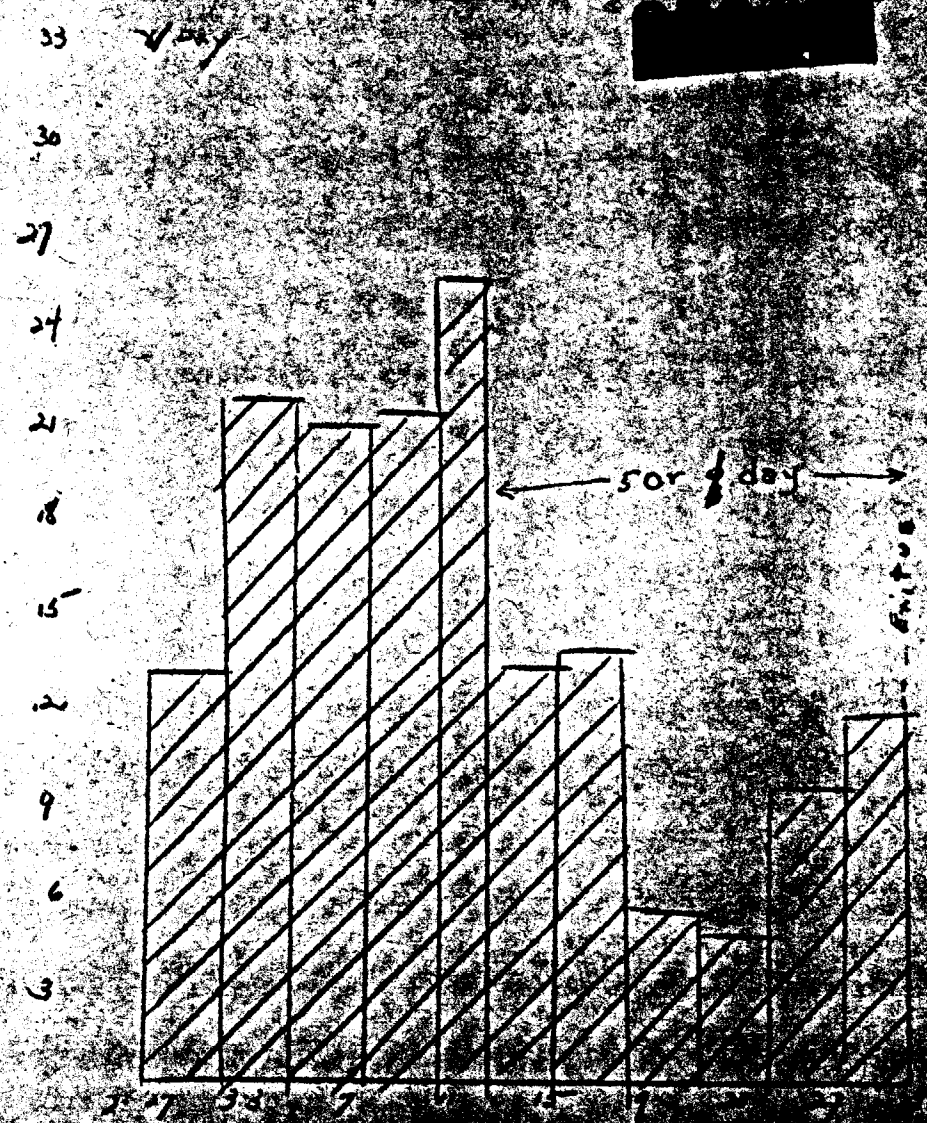

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Figure 2.
Urine Coproporphyrin in X-rayed Dog (#29)

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[redacted]

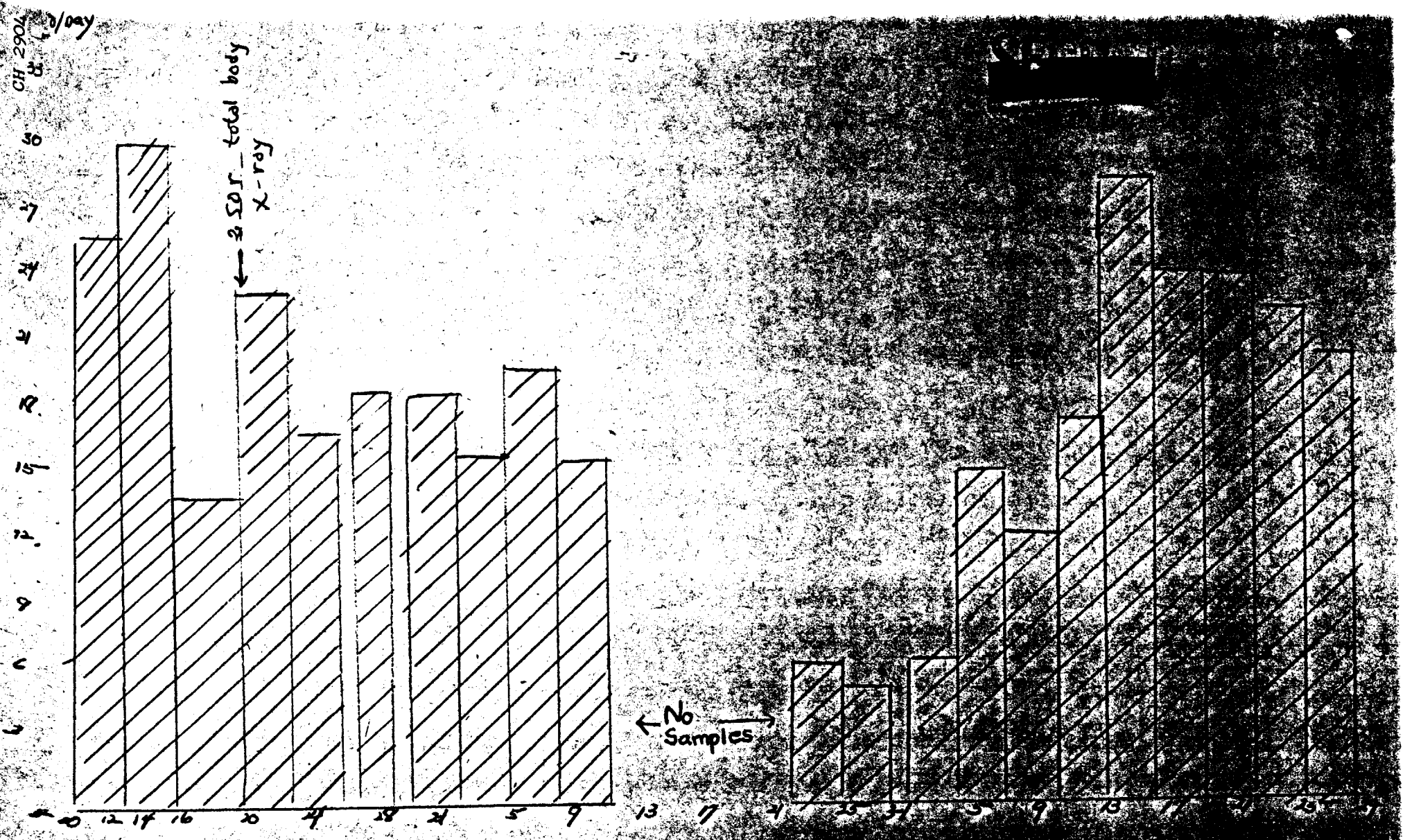

Figure 3

Urine Coproporphyrin Excretion
in
X rayed Dog (#24)

[redacted]

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CH29

[redacted]

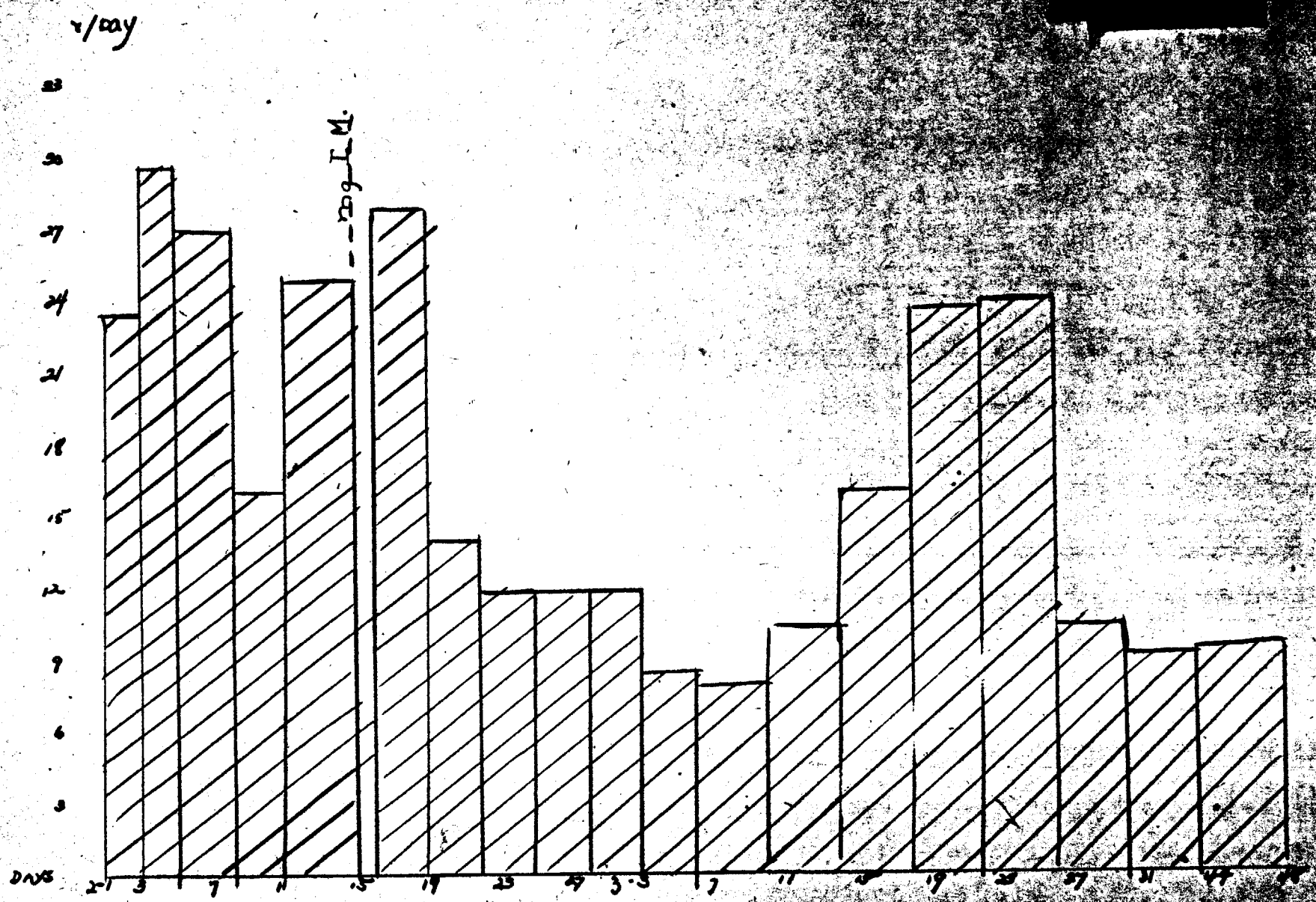

Figure 4

Urine Coproporphyrin Excretion in Product-treated Dog (#38)

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[redacted]

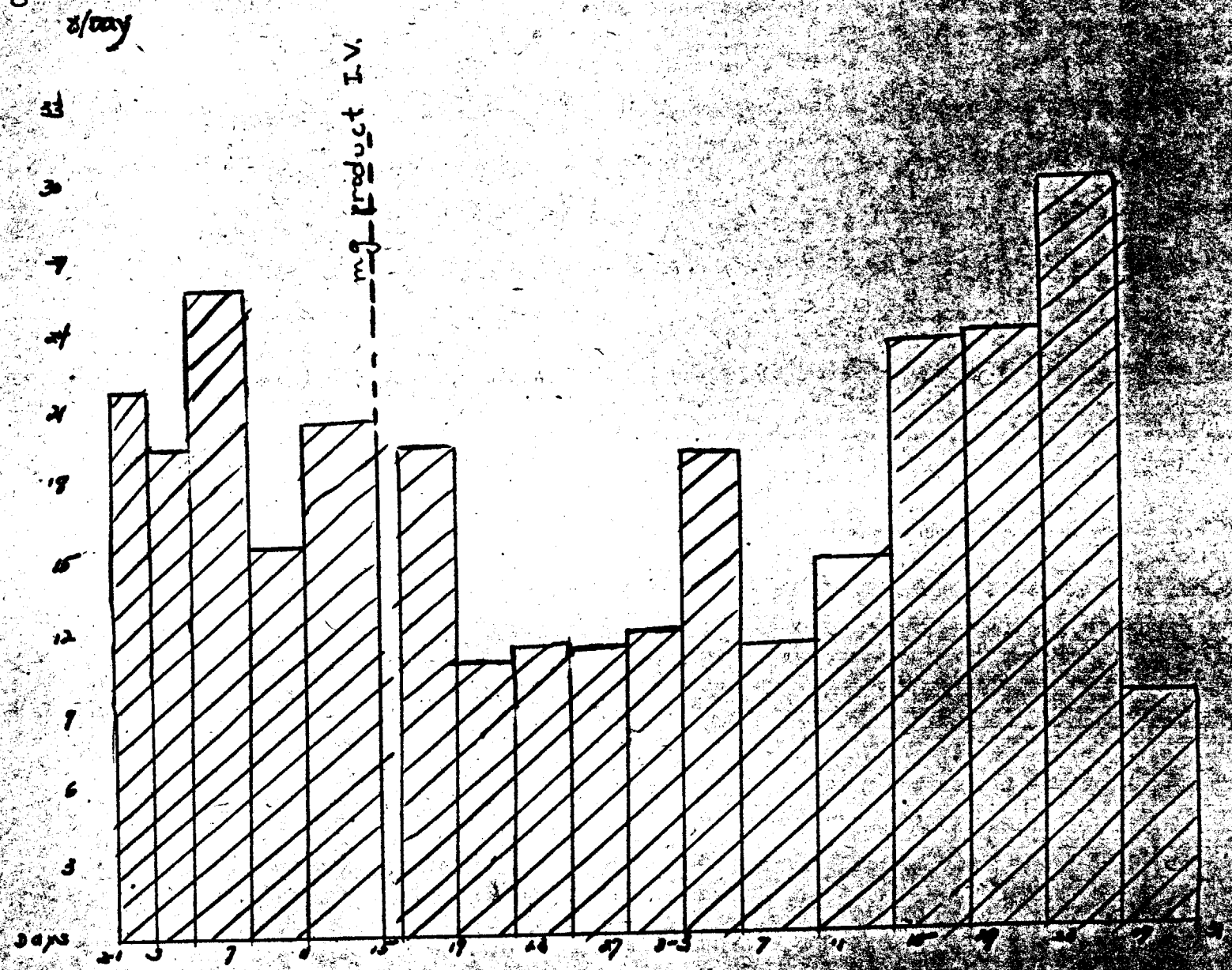

Figure 5

Urine Coproporphyrin Excretion
in
Product-treated Dog (#39)

[redacted]

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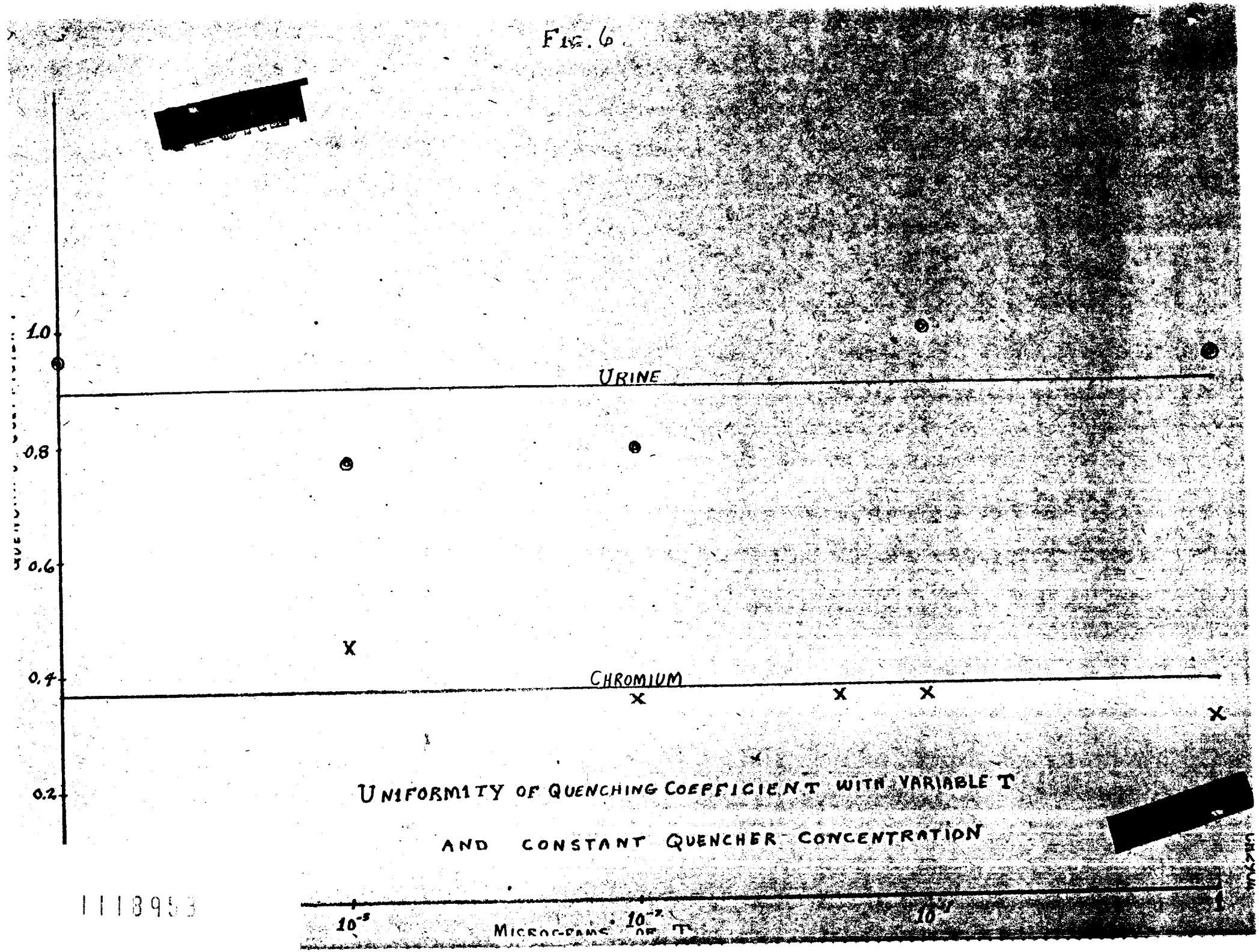
FIG. 6



UNIFORMITY OF QUENCHING COEFFICIENT WITH VARIABLE T

AND CONSTANT QUENCHER CONCENTRATION

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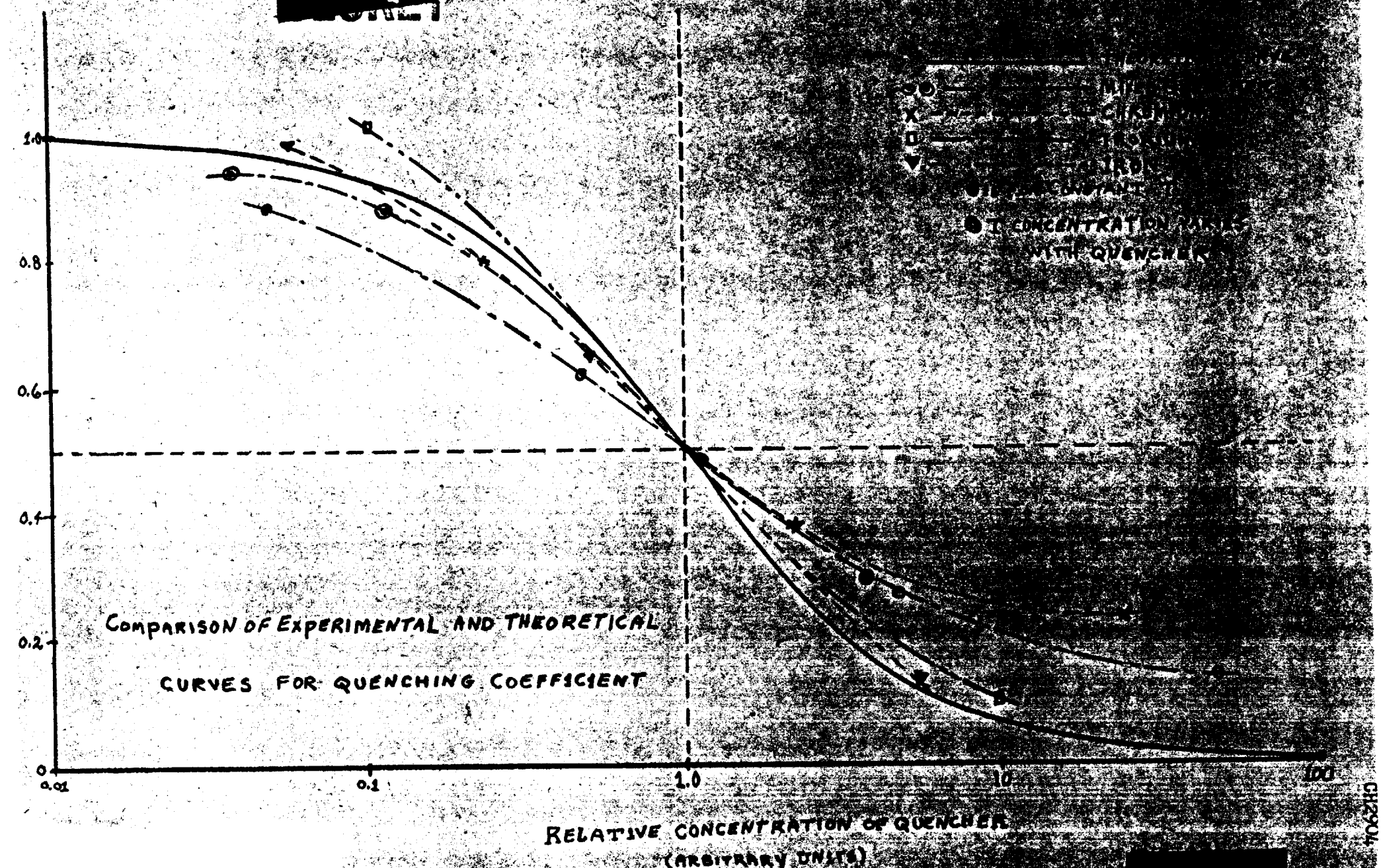
[redacted]

FIG. 7



COMPARISON OF EXPERIMENTAL AND THEORETICAL CURVES FOR QUENCHING COEFFICIENT

[redacted]

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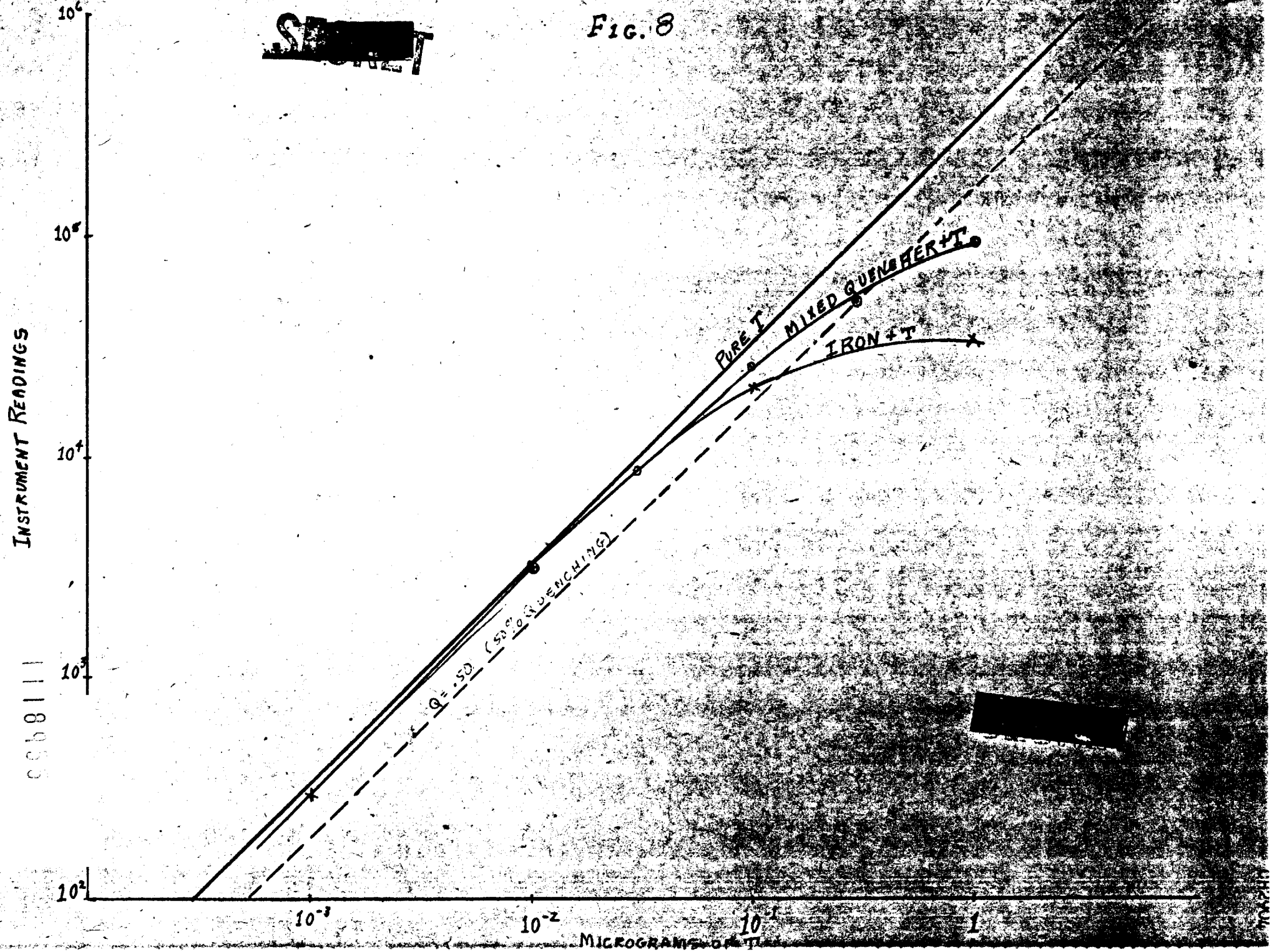
FIG. 8



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H-II Biological Research Section

K. S. Cole, Section Chief
C. Ladd Prosser, Assoc. Section Chief

244 MLH 2101 - Development of Inhalation Techniques

We have spent much time this month in testing the condensed spark as an aerosol source. This means of aerosol production has certain potential advantages over the arc--the low temperature may make possible aerosolization of molecules other than the oxide, and there is no carbon monoxide or cyanogen problem because the carbon does not burn appreciably. Reports in the literature (both project and otherwise) have indicated that it might be possible to quantitatively remove an added ingredient from a porous graphite electrode by means of a spark. We have carried out a series of experiments using a 15000 volt spark with 0.005 uF across a 3mm gap. The electrodes used were either ordinary spectrographic graphites or porosified graphites. The latter were made porous by heating at 500° for 1 hour. The following variations were tested.

1. Active material evaporated on surface of ordinary electrode
2. Drop of active material allowed to soak into porous electrode immediately before use.
3. End of porous electrode away from the spark is immersed in a solution of active material.
4. Drop of active material allowed to soak into spark end of porous ele electrode while other end is immersed in solvent.
5. Drop of active material allowed to soak into spark end of porous electrode while head of citric acid is put on opposite end to produce a constant flow of citric acid through the electrode.

To date our results with these various prodedures in the 1.4 li chamber have been variable, ranging from 1 percent to 15 percent of the material on the electrode being aerosolized. Work is continuing to increase yields and reproducibility. It might be noted that electron microscope photographs have shown a distinct difference between spark and arc particles. In the case of the arc one tends to get particles consisting of chains or agglomerates of smaller units so that many particles are in the 0.5 to 1 micron range altho they obviously consist of smaller units. This results from the fact that volatilization occurs at the high temperature of the arc, and the resulting vapor reaches cooler but highly ionized regions and condenses before any significant dilutions can occur. (In this connection it might be noted that the aerosol yield is doubled if one uses a 12 li chamber with a stream of air blowing through the arc in place of the static 1.4 li chamber). The spark, on the other hand, does not produce high temperatures and one gets only discrete particles which rarely exceed 0.1 to 0.2u in size.

244 MLH 2111 - Inhalation of Ruthenium Aerosol

Last month we reported the results of exposing rats to tracer amounts of RuO_4 vapor (carrier-free 330 day Ru). The active material left the lungs rapidly at first (over 50 percent in the first day) and then more slowly so that after a month the average half time for absorption is over 30 days. This type of phenomenon-an initial very rapid absorption followed by a slower one--had been previously observed in cases where the material as administered was rapidly

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absorbed but simultaneously a fraction of the material in the lung was reduced to a relatively non-absorbable valence state. To test that possibility with Ru, we have exposed rats to an aerosol of ruthenium chloride in which the Ru was in the +3, +4 state. The aerosol was produced by atomizing a neutral solution of Ru and drying the subsequent mist by admixture with dry air. 440 uc of Ru were atomized over a period of 2.5 houfs, and the rats breathed from the manifold described in previous reports. Analyses of the lungs of rats sacrificed at 0.1 and 5 days after exposure indicate that the Ru^{3-4} aerosol left the lung less than half as fast as the Ru^{8} vapor.

246 MLH 2536 Histopathologic effects of Radio-Cerium administered By Inhalation

Two additional rats were sacrificed at 68 days from the series exposed by inhalation to radio-cerium and previously reported as far as the 33-day sacrifice interval. The changes seen were similar to but more intense than those at 33 days. At 68 days there were many groups of hypertrophied septal cells extending in layers of single cells or thick masses along the surface of the septa and alveolar ducts. These masses seemed to radiate from foci and were not distributed throughout the lung. Nor were they arranged in such a pattern as to suggest their derivation by metaplasia from the bronchiolar epithelium. None of the numerous mitoses among the hypertrophied cells was distinctly abnormal.

The areas of acute and chronic inflammation of the pulmonary tissue were much more extensive than at earlier intervals. In places the inflammation was so intense as to obliterate the normal structure of the lung.

Although the areas of hypertrophic cells were distinctly abnormal in appearance and configuration, they showed no definite evidence of neoplasia. Further stages should be procured for study.

246 MLH 2721A - Late effects of Radioactive Strontium

It is now just a year since the original pilot series of 350 mice was injected, and certain findings may appropriately be detailed at this time.

The mice were divided equally between ABC (brown) and CF_1 mice. In each strain, four groups of 15 mice were treated by single doses and four groups of 20 mice each by monthly injection. Two control groups of 15 and 20 mice have also been maintained. The dosage levels in both single and repeated injection were 50, 10, 2 and 0.4 microcuries per mouse, or approximately 2, 0.4, 0.08, and 0.016 microcuries per gram. An attempt has been made to make definite diagnoses on all mice at death, but final diagnoses will have to be deferred until histologic study can be completed. Diagnoses given in this report are, therefore, tentative except in the case of osteogenic sarcoma, which could be reasonably well verified by radiographs and gross appearance.

The ABC (male) mice have been relatively very little reactive, and no findings of statistical significance have yet been encountered. Aside from a scattering of lymphoma, leukemia, and lung tumors (which are common in many strains of mice) one osteogenic sarcoma was seen in the group receiving 10 microcuries monthly and a malignant tumor, not yet diagnosed, in the group receiving 50 microcuries at a single injection.

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In the CF_1 mice, there is a hig. incidence of osteogenic sarcoma in the highest levels, a moderate increase in incidence of lymphoma, and no apparent influence on the incidence of lung tumors. In the accompanying table, the three highest dosages (50 microcuries in single injection and 10 microcuries and 50 microcuries in monthly injections) are grouped together, and lower levels are also combined. All incidences are expressed as percent of mice surviving the 150th day after first injection, as no animals died with tumors before that time.

Table 1. Tumor incidence in high and low level strontium^{89} mice, CF_1 strain.

	Number of mice in group	lung tumors	Percent with lymphoma and leukemia	osteogenic sarcoma
highest levels	39	15%	20%	26%
others	75	21%	5%	0
controls	29	10%	3%	3%

Radioautographs of four of the bone tumors have been made. In one the radioactive material was as concentrated in the tumor as in the ends of the bones, while in two there was very little radioactivity in the tumors. The two with high tumor radioactivity has been receiving reinjections.

The second table indicates the survival of the two strains of mice as a function of dose. The figures indicate days to death for one-half(median) and one-fourth (quartile) of the mice in each group.

Table 2.

Dose group	ABC male quartile	ABC male median	CF_1 female quartile	CF_1 female median
50 microcuries repeated	107	185	125	160
50 single	335	-	207	240
10 repeated	345	-	302	307
10 single	-	-	312	-
2 repeated	-	-	302	-
2 single	-	-	334	355
0.4 repeated	-	-	346	-
0.4 single	-	-	275	327
controls	-	-	292	-

Doses of 10 microcuries given at one time and of 2 microcuries repeated monthly in mice do not appear, after one year, to have produced any effect on survival or tumor incidence, in constrast to the higher doses administered. These findings will be presented in greater detail in an interim report.

246 MLH 2721C - Effects of radio-strontium and Yttrium on the skin

Since Strontium sulfate disappeares rapidly from the site of application and since the dosage can not readily be controlled, a series of rats has been given yttrium chloride by tattooing. Gentian violet and india ink have been used as

markers; the former does not persist satisfactorily in the area of application.

The technique of application is as follows: one or more single point applications are made with a commercial tattooing machine under controlled conditions as regards duration of application and depth of needle thrust. The immediate distribution of the injected material is in a volume not exceeding one cubic millimeter and extends into the dermis. The ten rats in the present group were measured by external counts and were sacrificed at the end of fourteen days, when the skin at the site of injection (mid-back), the inguinal and axillary lymph nodes, and the rest of the carcass were ashed for analysis.

Total retention in the body at two weeks was about 24-40 percent of the amount administered, and approximately one-half of this was found in the area of application. This area was receiving several thousand times as much radiation as was the body as a whole. Persistence of the radioactive material in the injected area showed a half-life of about five days; loss occurred through both absorption and desquamation.

In only one rat were gross skin lesions observed; at the end of a week small excoriations appeared at the sites of two tattoo marks and disappeared during the second week. Dosage calculations bases on external and ash counts and on the assumption that the radioactivity was evenly distributed through 5 cubic millimeters of tissue, show that the local areas received about 75,000 r during the first week and 15,000 r during the second week, when healing occurred. Obviously, the dose at the center of the area of application was probably still higher.

Rats given various amounts down to one-tenth of that noted above, uniformly showed at autopsy a single dilated vein entering each area, draining in the direction of the scapulae. These observations were not noted in control rats given the marker alone. In the three highest level rats a small circular area of erythema appeared between the third and eighth days around each injection site; No marked impairment of hair growth was seen, but this will be further investigated in sections of treated skin.

Radioactivity of the lymph nodes was never more than ten times (on a weight basis) that of the carcass as a whole, and in several instances was identical or nearly so.

246 MLH 2421 - The Effect of Sr^{89} and Splenectomy on Mouse Blood

A previous experiment was done on mice with Sr^{89} given by intraperitoneal injection. The haematological data from this experiment indicated that whereas a striking and sustained depression of the total leucocytes per mm^3 occurred (both lymphocytes and heterophiles), little or no change was seen in the hemoglobin in gms percent or in the number of red cells per mm^3 (RBC)

A comparable group of mice studied histologically showed striking degenerative changes in the bone marrow, but an early onset of increased hemopoietic activity in the spleen, especially erythropoiesis. The fact that anemia (reduction in Hgbln and RBC'S) did not develop was therefore considered to be due to the relatively long life of the erythrocyte and to any early compensation by the spleen.

An experiment to test this hypothesis was carried out as follows:
A group of splenectomized mice was given 40 μc of Sr^{89} intraperitoneally per mouse,

a group of non-splenectomized mice was given 40 μc of Sr^{89} intraperitoneally, a group was splenectomized but given no Sr^{89} and a control group was neither injected nor splenectomized. These groups have now been followed for 112 days.

The total leucocytes per mm^3 and the differential blood picture are essentially similar in both groups of animals receiving Sr^{89}. The hemoglobin in grams per cent and the erythrocytes per mm^3 have remained within the normal range in the groups with splenectomy alone, Sr^{89}, alone and in the untreated controls. The splenectomized animals injected with Sr^{89}, however, have become progressively more anemic up to 70 days, and thereafter recovery has been gradual.

142 MLH 2370 - Mouse Survival of Daily X-Ray

The method of analysis used for Drosophila survival and acute mouse survival shows that the damage accumulates with the exposure accumulation at each value of the daily dose and that the damage accumulates in the same fashion at 20, 80 and 200 r/day. The behavior at 40 r/day is typical, leading to the suggestion that at a given dose rate only those dose rates are effective which have recovery times equal to or longer than the mean survival time.

142 MLH 2510 - Histopathology of Single Exposures to X-Rays

The effects of 50 r x-radiation on rabbits were examined for comparison with the effects at lethal levels. This series was made up of eight experimental and four control rabbits, all of them males. Two experimental animals were sacrificed at each of the following post treatment intervals: 1, 3, 10, and 27 hours.

The small lymphocyte was the only cell type affected. It was not equally sensitive in all organs; almost all the small lymphocytes were destroyed in the germinal centers of the appendix, a smaller number in the lymph node and white pulp of the spleen, and practically none were destroyed in the thymus. The medium and large lymphocytes were not injured and none of the cells of the bone marrow were destroyed.

Lymph Node

One hour after treatment a few small lymphocytes were dead. Maximum cellular destruction was at 10 hours when approximately 20% of the small lymphocytes were dead. Damage was greatest in the germinal centers. Regeneration had begun at 27 hours but all the cells had not been replaced.

Spleen

The only cells damaged in the spleen were the small lymphocytes. Only a few were dead at 1 hour but approximately 50% of them were dead or dying at 3 to 10 hours and there were very few signs of regeneration at 27 hours.

Peyer's Patch

At 3 hours the germinal centers of the Peyer's patch contained many dead small lymphocytes. At 10 hours there were very few small lymphocytes left in the germinal centers. Regeneration had not begun at 27 hours. The small lymphocytes elsewhere in the Peyer's patch and the medium and large lymphocytes were not damaged.

Appendix

The small lymphocytes in the germinal centers of the appendix were more severely damaged than were those in any other region of the body. Dead small lymphocytes were present at 1 hour post-treatment time. At 10 hours there were large areas in the germinal centers which were made up almost entirely of dead cells and at 27 hours there were very few living small lymphocytes left. The other cell types were not damaged.

Thymus

This dose must be considered near the border line to produce visible alterations in the thymus since only occasional cells were damaged.

There were no changes in the bone marrow, testes, gut epithelium, lung, heart, kidney, adrenal, periphereal nervous system, skeletal muscle, bone and cartilage.

362 MLH 2520 - Histopathlogy of X-rayed Chickens

Three week old chickens were treated with 100 r total body x-radiation and sacrificed in pairs at the following post treatment intervals: ½, 2, 4, 8, 13, 24, 30, 48, 72 hours and 5, 8, 12, and 17 days. Significant changes were seen only in the bone marrow, spleen, thymus and nervous tissue. Damage was in general less than that previously reported after exposure to 400 r.

Bone Marrow

Mitotic activity was markedly reduced at ½ hour after treatment but at two hours had returned at least to normal. There were a few dead young erythroblasts and myelocytes at early intervals but this damage was slight compared to that following 400 r.

There were two periods of cellular depletion with no concomitant debris. The first such period was from 13 to 72 hours and a second and more severe one was seen at 8 to 12 days. Both erythroblasts and myelocytes were affected.

The significance of these periods of depletion if questionable for two reasons: 1) Occasionally sections of marrow from the un-treated chickens were nearly as aplastic as those of the experimentals in question. This similar "depletion" in the untreated chicken marrow is presumably due to the uneven distribution of hematopoiesis in the marrow cavity, and to the lack of uniformity in the region of femur marrow sampled at autopsy; 2) Depletion following 400 r occurred much earlier and was accompanied by considerable debris.

On the other hand depletion following a lower dose might be expected to occur at a later interval.

Spleen

At one-half hour, and more clearly at 2 hours, there was an increased number of dead lymphocytes in the white pulp. This debris was principally in the active nodules and in the margins of the sheaths. Debris was still in excess of normal

at 4 hours and 7 hours but not at subsequent intervals.

There was "clumping" of large lymphocytes at 2 hours; it appeared in varying amounts at subsequent intervals up to 18 hours.

There were no significant effects after the 18-hour interval.

Thymus

There was more than a normal amount of debris in the thymus at early intervals, especially in one 7-hour specimen. There were no significant changes after the 11-hour interval.

Nervous Tissue

Very occasional dead Schwann cells were present from 2 to 30 hours in the peripheral nerves and ganglia adjacent to the adrenal. Their number was greatest in the two 18-hour specimens. But, in the same specimens, the nerves near the thymus showed no changes.

At 48 hours and thereafter, the nerves appeared normal.

142 MLH 2410 - The Effect of 10r X-Ray on The Blood Counts of Mice.

Dougherty and White at Yale University have reported previously that they have obtained a lymphocyte depression within the first 24 hours in Strong CBA mice with X-ray doses as low as 10r. Their findings and explanation of the mechanism involved have already been reported in MUC-RSS 368 and MUC-RSS 384.

It seemed worthwhile to check the validity of such blood changes with doses of this low range on the strains of mice used in our laboratory. Male ABC mice were used. In order not to influence the blood picture by the blood loss involved in bleeding the same animals at all the counting periods involved, separate groups of 5 mice each were used to establish the individual hourly periods. Counts were taken at 1, 3, 6, 9, 12, 15 and 24 hours after the mice were given 10r total body. The controls were boxed and treated in an identical manner as the experimentals, with the exception of actual x-raying.

The lymphocyte curve obtained by Dougherty and White within the first 24 hours was U-shaped, the greatest depression being at the 6-9 hour period with a return to normal by 24 hours. Our mice failed to show this depression. There was a gradual fall in lymphocytes until 3 hours, then a steady rise until 15 hours, after which the counts returned to normal.

However, the control curve is identical with that produced by 10 r (except for one point, the 12 hour count), which leads to the conclusion that the effects exhibited certainly cannot be credited to the 10 r irradiation, but more likely to the handling of the mice, confining in boxes, etc.

142 MLH-2611, 2411, 2670, 1301 - Effects of Daily Doses of X-radiation on Dogs

Clinical Physiology - C. L. Prosser, M. E. Painter

One dog was given daily total body x-radiation of 50 r. During the same period blood samples were taken from a control dog and this dog placed in the exposure

chamber without having the x-ray machine in operation. The treated dog survived for 18 days after the beginning of treatment and accumulated 850 r. It lost weight steadily after the beginning of treatment and at the time of death its body weight had decreased by 28.3 percent. Food intake declined to near zero on the third day, rose slightly during the 4th to 6th days and from then on was very low. Water intake decreased from a control level of 800 cc/day to about 200 dc/day. Urine and feces output paralleled the decline in water and food consumption. The weight of the control dog increased by 500 gms during the three week observation period.

The dog which received 50 r daily maintained a constant rectal temperature until the 16th day when the temperature rose abruptly to above 40°C. The heart rate gradually declined from a control rate of 80/min to 55/min on the 15th day. Thereafter the heart rate rose rapidly and was above 200/min on the day of death.

The plasma volume remained essentially constant as judged by determinations made before treatment and 4 and 14 days after treatment began. The blood volume in the treated dog did decrease, however, by 20 percent, due to a decrease in hematocrit.

Plasma protein concentration and hematocrit values slowly declined by about 27 percent during the period of treatment. Hemoglobin values declined by 34 percent and the red blood cell count by 30 percent. Sedimentation rate was relatively constant but clotting time lengthened from 150 seconds before treatment to 300 seconds on the 16th day.

Hematology - L. O. Jacobson, R. Edwards.

The total number of white blood cells per mm^3 decreased rapidly and the white cell count on the 15th and 17th days were 50 and 25 cells per mm^3. The number of heterophiles fell from a control count of 4000 to zero on the 17th day. The lymphocytes decreased in number more rapidly than the heterophils during the first few days but thereafter the lymphocyte curve fell more slowly. The control dog from which the same amounts of blood were removed as from the treated dog showed no significant hematological changes.

Histamine - C. W. Hagen, Jr.

Plasma histamine determinations were made on both the treated and control dogs and showed no increase above control levels at any time.

Blood Chemistry - A. M. Brues, O. France.

Non protein nitrogen in the blood remained constant in the treated dog until the eleventh day when it decreased to half the control value and remained low until death. Nitrogen and phosphorus balance studies were made. As the food intake of the treated dog decreased the output of both nitrogen and phosphorus exceeded the intake so that the animal was in negative balance.

Pigment Excretion - S. Schwartz.

From the urine samples measurements were made of urine coproporphyrin excretion, urobilinogen excretion and excretion of other pigments. Urine coproporphyrin excretion decreased markedly during treatment and increased on the day before death. Urinary urobilinogen excretion also increased just before death. A green pigment was excreted in the urine of the treated dog. This pigment showed a maximum absorption at 632 mμ. Its identity is unknown.

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Fecal samples were analyzed for porphyrins, urobilinogen and hemochromogen. The percent concentration of the prophyrins and urobilinogen increased during treatment but because of the marked decrease in feces (44 to 7 gms daily) the total daily pigment excretion actually decreased. Blood was identified in the feces during the last week of life by a strong hemochromogen reaction.

Autopsy - H. Lisco

At autopsy the following observations were made:

Disemminated hemorrhages in skin, subcutaneous tissue, lymph nodes, skeletal muscles, diaphragm, myocardium, bladder and urethra, kidney pelvis, stomach and intestinal tract. Multiple ulcers in duodenum and jejunum, acute ulcerative and necrotizing ileitis with hemorrhages. Multiple thrombi in both lungs. Severe edema of right side of face and neck with extensive hemorrhages in subcutaneous tissue. Fatty infiltration of skeletal muscles and diaphragm. Extreme emaciation.

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Section III - Medical Hazards Section

J.J. Nickson, Section Chief
J.E. Rose, Associate Section Chief

241 MLH 3310 Building and Equipment Surveys For Beta Radiation - Rose, Wallace.

241 MLH 3320 Building and Equipment Surveys For Gamma Radiation - Rose, Wallace.

New Chemistry. During the past month the promptness of decontamination has diminished somewhat. As a result, the overall background of contamination has risen. The situation has been discussed with Chemistry Division personnel.

Argonne. The CP-3 room shows numerous areas of above tolerance radiation. These are guarded by appropriate signs or are roped off. Judging by the personnel monitoring devices, over-exposure is infrequent.

Eckhart. A complete survey of the building was done during the month. Above tolerance activities were noted in rooms 9,10,12,107,117,121, 313,404 and 415.

Ryerson surveys showed above tolerance activities in rooms 50,152, 256,351 and 352.

West Stands surveys continue to show many regions with high levels of activities of the routine working areas. Room 217 continues to be the worst offender.

Site B. Throughout the month room 103 has shown above tolerance activity levels. Mr. Greninger has been notified.

Site B Annex. As a result of new monitoring devices it has been shown that the radiation levels in room 172, the hot lab, may be as high as 500 r per hour. The solutions giving these activity levels have in the past been only partially handled with remote control devices. In the light of these measurements, over-exposure of personnel to the beta activity is certain. Because of this finding, instruments are being made which will permit substantially all of the work to be done without exposing the hands to the solutions. It

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is emphasized that this condition was detected only after suitable ionization chambers for measuring soft beta energies were developed. Surveys with earlier instruments failed to indicate even the order of magnitude of the hazard.

As before, many of the animals, their excreta, or their cages, show radioactivity. For the most part the levels do not exceed 30 mr/hr. In a few instances, particularly from excreta, readings of several hundred mr/hr have been obtained.

Armory. A tuballoy fire occurred in 101-D on 4/4/45. It started when a box containing tuballoy scrap was dragged across the floor. Over-exposure of personnel is not known to have occurred. Air measurements made in the room after the fire was out did not exceed the present permissible level for tuballoy in air.

241 MLH 3350 Personnel Monitoring of Beta Radiation - Rose, Wallace.

241 MLH 3360 Personnel Monitoring of Gamma Radiation - Rose, Wallace.

4670 pocket meter readings were made during the four week period ending April 10, 1945. 20 over-exposures were noted. This is 0.43% of the total number of readings. Eight of these readings, in the opinion of the exposed person or of the Health Division, were caused by radiation. Four are from the West Stands personnel.

It is of interest to compare the number of instruments worn in the various buildings of the laboratory. The figures for February and March are given:

Site	February	March
New Chemistry	786	799
West Stands	398	466
Site B	1879	1608
Eckhart-Ryerson	187	184
Argonne	1313	1613
	4563	4670

2200 films were developed and read. Three persons had shield readings greater than 0.6 for one week.

1280 hand counts for beta or gamma activity were scheduled. 1017 or 79% were done. 23 or 1.8% high hand counts were recorded. 13 were from Hindman's and Stewart's groups in the Chemistry Division.

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All laundry continues to be monitored for beta or gamma radioactivity before it is sent to the laundry. Those articles which show greater than 800 counts per minute are sent to another site which is equipped to launder contaminated clothing. During the past month approximately 20 articles were sent to this site.

000 MLH 3300 Decontamination Squad - Gardner, Nickson.

During the past month the following areas were decontaminated:

Service Building
Kent 101,104,109,112 and 301
Jones 401, attic
Armory 203
Eckhart 2,9,10,11 and 12
Ryerson 256

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CONTRACT # W-7405-eng-48-A

Joseph G. Hamilton, M.D.

A. TECHNICAL PROGRESS REPORT ON THE METABOLIC STUDIES OF FISSION PRODUCTS

1. Soil Studies

On april 2, 1945, pea plants which had been grown in active W topsoil were harvested. The plants were approximately three months old. Soils activated with the following radio-elements had been used in the experiment: Y, Ce, Zr + Cb, and Sr. Each plant was grown in a pot containing 2.5 kg. of soil. The mean activities of the various soils for the three months period was as follows:

Y - .145 μ c/gm
Ce - .212 μ c/gm
Zr + Cb - .125 μ c/gm
Sr - .166 μ c/gm

The plants have been separated into roots, stems, leaves, pods, and seeds and quantitative determinations of activity are being made. Qualitatively it can be said that all plants showed radiation injury. This was particularly marked in the case of both the roots and tops of the Sr plants. This was probably due to the large absorption of Sr by the plants. The Y, Ce, and Zr + Cb plants showed definite signs of root injury, particularly the Ce plants.

A sample of radio-tellurium was received from X-10 and purified. The absorption of Te* from clay by barley plants was studied. Barley plants were immersed for 24 hours in 0.01% Ca-bentonite suspensions containing radio-tellurium. The fractional uptake of activity was as follows:

Number	%Activity in Leaves	%Activity in Roots
1	.0472	31.2
2	.0397	41.8
3	.0377	38.5

On the basis of these results, it appears that the behavior of Te is similar to that of Y and Ce in its absorption by plants. Longer term experiments are in progress. The absorption of radio-tellurium on Ca bentonite clay was measured with the following results:

Conc. of Clay Suspension (%)	% of Activity Adsorbed
.01	30.2
.02	65.8
.05	81.1
.10	87.0
.50	89.8

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These results show that Te is similar to Sr in its adsorption on clay although its absorption by plants from clay suspensions is markedly different from that of Sr.

Experiments dealing with the decontamination of active soils and the migration of radio-elements in soil are being continued.

2. Radio-Iodine Studies

Recent studies were undertaken to determine the blocking effect of inert Iodine upon the uptake by the thyroid gland of I^{131}, free from inert carrier. Rats were the experimental animals employed in these studies, there being three animals used for each group. Two series of experiments were done, employing four groups of rats for each series. Three dosage levels of the inert Iodine were used, namely 1, 10, and 100 mg. per kg. of body weight. In each series, a fourth group received only the carrier-free Iodine and thus served to act as a control. The inert Iodine and carrier-free Iodine were given by intramuscular injection at the same time, the animals sacrificed four days later, and the thyroids assayed for their uptake of I^{131}. The following table summarizes the average results obtained in these two series of experiments.

TABLE I

The % Uptake of I^{131} by the Thyroid Gland of the Rat, 4 Days After the Intramuscular Administration of Carrier-free I^{131} and, I^{131} Containing 1, 10, and 100 mgm per kg. of Body Weight.

	Carrier-free	1 mgm I^{127}kg.	10 mgm I^{127}kg.	100 mgm I^{127}kg.
Series A	4.82	2.06	.96	.20
Series B	7.46	3.06	.99	.32

As can be seen from the table, a very sharp decrease in the amount of Iodine accumulated by the thyroid takes place as the dosage of of inert Iodine increases. However, it is rather significant that even with as much as a 100 mg. of inert Iodine per kg. a quite significant amount of the labled Iodine is capable of entering the thyroid gland. Another interesting observation is to be made from these results, namely, that the amount of Iodine taken up by the thyroid of the animals receiving no inert Iodine is surprisingly low when compared to figures given by Chaikoff (CH-2257). These relatively low uptakes by the thyroid of carrier-free Iodine are comparable to the figures secured at Chicago in studies where carrier-free Iodine was administered by inhalation. We suspect that this factor is due to the possible presence of quite appreciably quantities of Iodine in the diets employed here and at Chicago. The uptake observed in the other groups receiving varying amounts of inert Iodine agree surprisingly well with the compiled data given in CH-2257. We are now setting up new groups of animals which will receive at weekly intervals the three

dosage levels of inert Iodine employed here for a period of four weeks. One week after the last administration of inert Iodine, the animals, together with the appropriate number of controls, will be given the carrier-free Iodine. These experiments are being set up for the purpose of determining the blocking effect of repeated doses of inert Iodine. This will duplicate the situation which would normally exist where personnel exposed to this substance would be given prophylactic protection by the administration of inert Iodine.

3. Smoke Studies

A series of smoke studies, in which aerosols containing fission product have been produced by a new procedure, are reported in another section. In addition to these experiments, a series of studies are now under way in which Uranium-free fission products without inert carriers, will be volatilized by means of a carbon arc and rats exposed to the resultant aerosol in the usual manner.

4. Projected Studies

The soil, smoke, plant, and radio-Iodine studies are to be continued.

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[redacted]

April 20, 1945

N. C. I.

R. R. Spencer, Chief

BIOLOGIC ACTION OF X AND GAMMA RAYS

I. Continuous exposure for 8 hours daily

Original mice and guinea pigs (daily doses 4.4 r, 2.2 r, 1.1 r, and 0.11 r).
Approximate total doses: 3350 r, 1675 r, 840 r and 88 r.
(Additional acute exposures not added).
Rabbits (daily doses 8.8 r, 4.4 r, 2.2 r, 1.1 r, and 0.11 r).
Approximate total doses: 5500 r, 2750 r, 1375 r, 680 r and 68 r
(additional acute exposures not added).

Term experiments

Mice: (daily doses 8.8 r, 4.4 r, and 1.1 r).
16 and 14 months: total doses 1020 r, 510 r, and 120 r.
12 and 10 months: total doses 620 r, 310 r and 70 r.
8 and 6 months: total doses 90 r, 45 r, and 12 r.
Inbred guinea pigs of family 2 (daily dose 8.8 r) total dose 740 r.

The following table gives the survival data on the experimental and control LAF_1 mice.

Due to the small number of animals in each group it is difficult to draw conclusions especially as infectious and sever eczema favored certain cages. It seems, however, that up to and including the 1.1 r level the average life span of both sexes is not shortened. It is surprising that this seems to hold true for the 1.1 r level, as there exists an increase in the incidence of malignant lymphoma and as ovarian tumors are induced in all groups of this level. The life span of the groups on the 2.2 r, 4.4 r, and 8.8 r levels is definitely decreased, this, however, is mainly due to the increasing incidence of malignant lymphoma and ovarian tumors. Due to this increase in tumor incidence it is extremely difficult to draw general conclusions from these data as to the effects of chronic radiation on life span if no tumors are induced.

Survival data for the hybrid guinea pigs of the original experiment are essentially the same as those given in the February report.

All rabbits are alive except one (exposed to an acute dose of 50 r) which died of intercurrent disease as previously reported.

During the month 3 mice died and 6 were killed in moribund condition. Two of the 3 which died had severe eczema and one had polycystic kidneys. All were males, 2 exposed on the 1.1 r level and one on the 0.11 r level. Three males and 3 females were killed and autopsied. One of the males

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[redacted]

Animal Group	Sex	Initial number	Survivors	Age
Control (I)	m	8	8	28½
Control (I)	f	8	4	28½
Control (II)	m	8	3	26 3/4
Control (II)	f	8	2	26 3/4
Acute exp. 12.5 r	m	8	4	29 ½
Acute exp. 12.5 r	f	8	2	29 ½
Acute exp. 50 r	m	8	none	(29 ½)
Acute exp. 50 r	f	8	1	29 ½
0.11 r	m	8	5	28
0.11 r	f	8	3	28
0.11 r plus acute exp. 12.5 r	m	8	5	28
0.11 r plus acute exp. 12.5 r	f	8	6	28
0.11 r plus acute exp. 50 r	m	8	1	28
0.11 r plus acute exp. 50 r	f	8	3	28
1.1 r	m	8	3	26 3/4
1.1 r	f	8	2	27 ¼
1.1 r plus acute exp. 12.5 r	m	8	none	(26 3/4)
1.1 r plus acute exp. 12.5 r	f	8	4	27 ¼
1.1 r plus acute exp. 50 r	m	8	5	26 3/4
1.1 r plus acute exp. 50 r	f	8	3	26 3/4
2.2 r	m	8	2	27 1/4
2.2 r	f	8	6	27 ½
2.2 r plus acute exp. 12.5 r	m	8	none	(27)
2.2 r plus acute exp. 12.5 r	f	8	1	27 1/3
2.2 r plus acute exp. 50 r	m	8	2	27
2.2 r plus acute exp. 50 r	f	8	1	27 ¼
4.4 r	m	8	1	27 ½
4.4 r	f	8	1	27 2/3
4.4 r plus acute exp. 12.5 r	m	8	1	27 1/3
4.4 r plus acute exp. 12.5 r	f	8	none	(27)
4.4 r plus acute exp. 50 r	m	8	none	(27)
4.4 r plus acute exp. 50 r	f	8	1	27 ½
8.8 r (300 r)	m	8	2	27 2/3
8.8 r (300 r)	f	8	1	27 2/3
8.8 r (680 r)	m	8	1	27 2/3
8.8 r (680 r)	f	8	2	27 2/3

The last animal of the 8.8 r groups, continuously exposed, was killed in moribund condition at the age of 24½ months.

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was exposed on the 1.1 r level, it showed at autopsy malignant lymphoma of the spleen. The second was exposed to 680 r on the 8.8 r level at the age of 3 to 5 months, the main gross finding was polycystic kidneys. The third had received an acute exposure of 50 r in 5 hours at the age of approximately 5 months; it showed grossly at autopsy eczema, nephritis and an abscess of the preputial gland common in old males. One of the females that was killed and autopsied was exposed to 0.11 r, it showed grossly malignant lymphoma; the second one was exposed to 0.11 r and an additional acute exposure of 50 r it showed grossly ovarian tumors and a subcutaneous tumor of the left pectoral region; the third was exposed to 1.1 r and an additional acute exposure of 12.5 r. It showed grossly bilateral ovarian tumors.

It was reported last month that the experimental strain A mice exposed on the 8.8 r level and killed and autopsied at an average age of 11 months after a total dose of 2500 r, showed an increase in lung tumor incidence over that of the controls of the same age. The examination of the histological material confirmed this. The lung tumor incidence of the controls was approximately 50% (corresponding to that found previously by Heston for strain A mice of approximately the same age) while that for the experimental animals was approximately 75%. Furthermore the average number of nodules of the controls with tumors was 1.23 while that of the irradiated mice was 1.73. This difference is statistically significant. It must be emphasized that strain A mice are the most susceptible animals known for spontaneous lung tumors and that the incidence of lung tumors will increase considerably when e. g., carcinogenic hydrocarbons are injected subcutaneously in doses of a fraction of a milligram. It is impossible in this case to detect the presence of the hydrocarbons in the lungs of these mice by spectrographic analysis although this method will show the presence of as little as 10^{-8} gm. in one pair of mouse lungs. The chronic dose to which these mouse lungs were exposed was 2500 r given within approximately 300 days, a dose to which lungs of man will hardly be exposed chronically. Considering further that man is considerable less susceptible to spontaneous lung tumors than mice it can be stated with reasonable certainty that the increase in lung tumor incidence produced by chronic irradiation in man will probably be extremely light and may not even be detectable.

II. <u>Breeding experiments</u>

Counts of premordial, growing, and atretic follicles in serially sectioned ovaries were made to ascertain whether the decrease in litter size in certain groups of irradiated breeding LAF_1 females was due to a decrease in the number of follicles present or to chromosomal changes (dominant lethal mutations). Counts were made on the following groups, groups receiving total doses of 880 r and 770 r at the rate of 8.8 r per day and at the rate of 8.8 r per 8 hours per day and the group receiving a total dose of 770 r at the rate of 4.4 r per day. The results are presented in the following table and indicate that the reduction in litter size in the present experiments could be due to a reduction in the number of follicles present. For comparison counts which have been made on normal rat ovaries

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Table II

Dose Rate	Total Dose	Average Litter Size	No. of Animals	Age (Months)	Average Number of Follicles		
					Permor-dial	Grow-ing	Atretic
8.8 r/day	880 r	2.6	6	7-9	0.16	2.5	0.66
"	"	---	9	12-14	0	0	0
"	770 r	6.1	8	7-8	0.37	9.9	0.75
"	"	---	13	13	0	0	0
8.8 r/8 hrs.	880 r	2.5	3	4-7	0	4.6	1.6
"	770 r	5.0	2	7	0	2.5	2.5
4.4 r/day	770 r	2.6	2	8-9	0	4.5	3

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indicate the presence of approximately 35,100 ova in both ovaries at birth, 11- 10,000 at 23 days and 63 days, 6,000 at 70 days and 2,000 at 31 months. (Biology of the Laboratory Mouse by the Staff of The Roscoe B. Jackson Memorial Laboratory, Chapter 2.)

III. Hematology

The blood picture of the surviving control and experimental LAF_1 mice is the same as previously reported. Differences observed are slight and may be due to disease or tumor formation rather than a radiation effect on the hematopoietic system. The red count in all groups varies between 7 and 10 millions with the exception of the 4 surviving mice of the 4.4 r per 8 hours level in which it is slightly lowered (5.6 to 7.6 millions). The platelet count of the controls and most of the experimental animals lies between 800,000 and 900,000. Some animals of the 1.1 r and 2.2 r groups have counts as low as 500,000, on the other hand the four surviving mice of the 4.4 r groups (total dose 3350 r), have platelet counts within the limits of the controls. Total white counts are high in many animals especially the males (10,000) frequently associated with a high neutrophil count. A few animals show high total white counts (30,000) with a lymphocytosis indicating leukemia.

The blood picture of the surviving control and experimental hybrid guinea pigs is as follows: The 0.11 r and the 1.1 r groups and those exposed for 1 or 2 months respectively on the 8.8 r per 8 hours level show a blood picture comparable to that of the controls. The slight decrease in number of platelets of some of the animals of the 1.1 r groups reported last month was not observed this month. Two of the animals of the 2.2 r groups show lowered red counts (3.0 to 3.6 millions) and lowered platelet counts (150,000); in the remaining animals all counts are normal to slightly below normal. In the 6 surviving guinea pigs of the 4.4 r per 8 hours level counts range as follows: Red count 3 to 5 million, platelet counts 26,000 to 140,000 and total white counts 2000 to 9000.

The inbred guinea pigs, exposed on the 8.8 r per 8 hours level (total dose 740 r) show normal red counts, lowered platelet counts (1000,000) and total white counts between 3,000 and 4500.

The blood picture of the rabbits is as follows: Control animals and experimental animals up to the 4.4 r group have comparable counts: red count 5.8 to 6.4 millions, platelet count 200,000 to 300,000 and total white counts of 4500 to 7000. In the animals of the 8.8 r group the red count is slightly lowered 5.2 to 5.6 millions, in two animals the platelet count is lowered 100,000 and 140,000 in the third it is normal. The total white count is 3300 to 7500. In all experimental animals of the 1.1, 2.2, 4.4, and 8.8 r groups there is an increase in percent neutrophils, increasing with total dose and resulting in reversal of the differential count in the animals of the 8.8 r group.

IV. Pathology

Tissues have become available for histologic study on the following mice. One on the 8.8 r per 8 hours per day level (total dose approximately 5800 r); three on the 4.4 r per 8 hours per day level (total doses 2800 to 3000 r); five on the 2.2 r per 8 hours per day level (total doses 1400 to 1500 r); two on the 1.1 r per 8 hours per day level (total doses 700 to 750 r); two on the 0.11 r per 8 hours per day level (total dose approximately 80 r); and three control animals.

Earlier in the experiment lymphomas were seen most frequently in animals exposed on the 818 r, the 4.4 r and the 2.2 r per 8 hours per day level, while the incidence in animals exposed on the 1.1 r and the 0.11 r per 8 hours level was approximately the same as in control animals. This order of incidence is now reversed, supporting the thesis originally set forth that the effect of the radiation is to decrease the tumor development time or "latent period" and hence cause them to appear at an earlier age than they would spontaneously. This suggests that these lymphomas may not be primarily induced by the radiation. This is in contrast to the hypothesis that leukemia in mice is primarily induced by the radiation. The possibility exists that a mere reduction of tumor development time of "spontaneous" leukemia plays an important role in the induction of so-called radiation leukemia.

Loss of follicles in the ovaries with the development of ovarian tumors continues to appear without exception in animals exposed on the 8.8 r, the 4.4 r, the 2.2 r and the 1.1 r per 8 hours per day levels. These changes have been observed on the 0.11 r per 8 hours per day level only in those animals that received in addition an acute exposure of 50 r and recently also in those animals that received in addition the acute exposure of 12.5 r.

Definite testicular atrophy continues to be seen only in animals exposed on the 8.8 r and the 4.4 r per 8 hours per day levels. One mouse that had been exposed on the 8.8 r per 8 hours per day level for a total dose of approximately 5000 r and had been removed from the field three months before autopsy showed active spermatogenesis in the testis. This indicates that this tissue, though severely damaged over an extended period of time, can recover.

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B. V. A. Low-Beer, M.D.

Four patients with arthritis and one with chronic myositis were exposed to total body x-ray at 1000 KV. Approximately 20 r at the surface of the body was given daily until three of the patients received approximately 300 r and two patients received approximately 280 r. In addition to careful clinical observation complete blood counts were done on the patients before, during and after the above treatment. No untoward symptons resulted. Clinical and laboratory observations are still in progress.

The x-ray therapy in this group of 5 patients was completed only in mid November 1944,but a few significant alterations in the hematological picture have occured. In all a moderation reduction in the leukocyte per mm^3 was apparent at the time the therapy was completed or within two weeks thereafter. This represented a reduction in both neutrophils and lymphocytes but particularly of lymphocytes. In none was a reduction of leucocytes per mm^3 alarming. The lowest figure reached was 3800.

A moderate shift to the left occurred in the neutrophils of only one of the patients studied. The number of monocytes per mm^3 were at the upper limit of normal during control observation and varied considerably during and after treatment. In one case however an absolute monocytosis occurred near the end of therapy and persisted for several weeks. This monocytosis probably does not represent the "classical" monocytosis reported by various authors after chronic exposure to x-ray or radium, but rather the response of the underlying disease process to the x-ray therapy. Dr. R. S. Stone. in previous summary reports on patients treated in a similar manner but with 200 KV x-rays, and observed for more than a year, found comparable hematological changes with recovery. The post irradiation monocytosis referred to above was a frequent observation in the patients he reported, and persisted for long periods; the patients were largely arthritics.

No clear cut effect was seen upon the number of platelets per mm^3 in the patients reported here. The effect of the x-ray therapy upon the erythrocytes per mm^3 and hemaglobin in grams per 100 cc of blood is rather difficult to evaluate. In only one patient was the reduction of the erythrocytes per mm^3 significant. This reduction became apparent six weeks after cessation of therapy and reached its maximum three months after completion of the x-ray therapy.

These patients are continuing under observation and a subsequent report will be given.