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N. C. I.

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REPORT FOR MONTH ENDING NOVEMBER 30, 1944

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Table of Contents

		Page
A.	Abstracts	2
B.	W - 7401 - eng - 37	
	H - I	6
	H - III	15
	H - II	18
C.	N. C. I.	27
D.	7401 - 37 - 2	31
E.	7401 - 37 - 13	33

Report received: December 12, 1944; Figures received: January 4, 1945
Issued:
JAN 13 1945

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A-00167

Human Subjects Project

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The total white count of rats was lowered by Sr^{89} using injected doses of 0.25, 0.62 and 2.5 μc/gm. Doses of 5 μc/gm by stomach tube affected the number of heterophils similarly to 2.5 μc/gm given intraperitoneally but had less effect on the number of lymphocytes.

Fission mixture by stomach tube in doses of 1.7 ,.7 and 27 μc/gm depressed the level of the lymphocytes. It depressed heterophil level in doses of 7.0 and 27 μc/gm.

A significant number of lymphomas are appearing in mice injected once with Sr^{89} in doses of 2.5 μc/gm last April. Breast tumors are being seen in rats which were giv en single or repreated doses of x-ray, starting 8 months ago.

Rabbits surviving total body exposure to 800 r of x-rays show nearly normal histology except in the ovary and testis, 31 days after treatment.

Exposure of rabbits to fast neutrons (cyclotron) caused a rise in the number of heterophils for 24 hours and a subsequent fall; the number of lymphocytes was lowered 3 hours after treatment. The decrease was roughly proportional to the dose from 8 to 70 n. Above the latter dose no greater decrease was observed.

Medical Industrial Hazards Section

A final report on special health hazard surveys and reco mendations made at the Quality Hardware Company (subcontract recently terminated) has been written. Health hazard inspection visits to Revere Copper and Brass Inc. and the Ames laboratories made during the past month are discussed in MUC HG 825 and 826 respectively.

Of 40 finger print impressions of Metallurgical personnel taken and analyzed during the past month 39 were normal, one abnormal.

The Tuballoy and TX contamination at Site B coming from the burnout furnaces has been partially solved by installation of filters in the exhaust line from the furnaces.

63 of 99 pocket meter readings above 0.1 r per day for the month ending November 11, 1944 were felt to be valid readings. Only one badge meter during this same period had a reading of 0.6 for a week.

U. of California Radiation Laboratory

The radio-autographic and tracer smoke studies with U_3O_8 smoke containing fission products are being continued. An assay of carefully cleaned algae from the settling basin at the site revealed that no striking selective localization of any specific member of the fission products took place. Further studies of the recently reported observations of the high degree of deposition of Sr, Y, Zr Cb, and Ce indicates that this effect is real and not simply due to adhesion of clay particles to root surfaces. Studies concerning the fixation of fission products on various types of soils with particular reference to those existing in the Hanford area are now in progress.

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I. ABSTRACT

Clinical Medicine and Medical Research

After an acute exposure of rats to 100 r of xray irradiation, the O_2 uptake of the testes was inhibited as early as four hours after irradiation and was still manifest twenty-one days after irradiation. Anaerobic glycolysis and the oxidation of succinate was not affected.

$TO_2(NO_3)_2$ has no effect on the activity of glucose oxidase. Hydroxy-aspartic acid brings about complete reactivation of succinoxidase on addition of twenty-equivalents per equivalent of TO_2^{++}; citric acid under the same conditions produced a reactivation of seventy-two per cent. The inhibition of glucose oxidase in baker's yeast was ninety-three percent reactivated upon the addition of ten equivalents of citrate per equivalent of TO_2^{++} and eighty-eight percent upon the addition of hydroxy-aspartic acid. When TO_2^{++} was added to human serum and the protein components were separated by electrophoresis, TO_2^{++} was found in the albumin and in the globulin fractions. It would appear that TO_2^{++} combines with both these components of serum protein.

One hundred and thirty-eight physical examinations were performed in the past month, eighty-six of which were pre-employment examinations and fifty-two on transferring personnel. One individual was rejected for employment because of physical abnormality. The number of visits to the health service for occupational and non-occupational illness or injury has increased from five hundred and fifty-three in September 1944 to seven hundred and six in November 1944.

A total of 4596 clinical laboratory examinations were performed on Metallurgical personnel from October 15 to November 15, 1944. This included the initial examinations of sixty-six new employees and regular follow up examinations of nine hundred and fifty-five regular employees. No clinical laboratory abnormalities were considered to be secondary to work hazards.

Further urine catalase studies on personnel exposed to T revealed no significant difference between individuals with relatively heavy T exposure and those with little or no T exposure.

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Biological Research Section

A static aerosol exposure chamber has been designed and constructed. Twenty-eight rats can be exposed at one time. A test run has been made with radioactive cerium which was dispersed from carbon arcs. Thermal precipitator samples showed that 18 percent of the material was dispersed as an aerosol; this disappeared from the chamber with a half life of thirteen minutes.

Radioactive yttrium was more toxic for rats than other fission elements which have been investigated. The mid-lethal dose (intracardial injection) was below 2 μc/gm.

Zirconium^{93} in equilibrium (50-50) with Columbium^{93} was injected intracardially into rats. This equality was maintained in most tissues except for a higher proportion of columbium in muscle and urine. A method has been developed for ascertaining relative percentages of Zr^{93} and Cb^{93} from two points on the absorption curves.

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National Cancer Institute

Mice: 0.1 r per day (8 hours), Total 66 r: These mice and many of the controls are showing WBC's between 10,000 and 20,000 - believed due to infection of an unknown type. Other experimental groups show this change infrequently.

1 r and 2 r per day (8 hours), Totals 625 r and 1250 r: RBC, platelet count and hemoglobin content, similar to controls.

4 r and 8 r per day (8 hours), Totals 2500 r and 5000 r: RBC,platelets and hemoglobin lowered.

Lymphomata: 12 new ones during month; total of 58 to date;22 of these in the 8 r per day (8 hours), 9 in the 4 r and 9 in the 2 r per day (8 hours) group, 4 in the controls and scattered ones in other groups.

Strain A mice - 8 r/day (8 hours). Present total of 1550 r: White counts considerably lower than controls.

Guinea pigs: (1) Hybrid: 0.1 r/day to 66 r total, 1.0 r/day to 625 total. Counts same as controls.
2 r/day to 1250 r total and 4 r/day to 2500 r total. All counts lowered; platelet counts most. One in 4 r/day level killed with aplastic anemia.

(2) Inbred - family 13 - 8 r/8 hour since May 1944. All counts lowered. Four with total doses of 1600 r autopsied on account of aplastic anemia.

Rabbits: 8 r/day to total of 4100 r; 4 r/day to 2050 r; 2 r/day to 1025 r; 1 r/day to 512 r; and 0.1 r/day to 50 r; Lymphopenia increasing with increasing total doses.

Pathological Data, Mice: 8 r/day (8 hours) total of 4500 r, 2 males showed extreme testicular atrophy but a few spermatogenic elements remained.

4 r/day (8 hours) to total of 2500 r; 1 female had ovaries devoid of follicles but no other significant change.

No one marrow atrophy in these three animals.

Michael Reese Hospital

Mice fed 10 mg of T as the nitrate in the daily ration (0.5% T nitrate in diet) showed no evidence of T intoxication at any time during an experiment lasting one year. Mice which received 20 mg daily in the diet (10% T nitrate in diet) developed an acute intoxication during the first three weeks with loss of eight. A few animals died during this period and showed cloudy swelling of the kidneys or an acute necrotozing nephrosis. Mice which survived this period, recovered more or less completely and at end of one year showed no signs of toxicity of significant pathological change except they weighed about 15% less than the control mice. Mice receiving 80 mg of T nitrate daily in the diet (4% T nitrate in diet) showed a similar but more severe intoxication in the first three weeks with more deaths occurring and more severe

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pathological changes apparent in animals which died. Following this initial period of severe intoxication a state of subacute intoxication prevailed; the animals ate less food, weight loss was invariable and scattered deaths occurred up to 64 days when the animals were sacrificed for T analysis and pathological study.

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000 MLH 1100 EMPLOYEES HEALTH SERVICE - J. Garrott Allen, M.D.

The activities of the clinical group of the Health Division operating in Drexel House for the period October 15, to November 14, 1944 are shown in the following tables.

Physical examinations		
Academic	56	
Non-academic	82	
Total (52 for transfer purposes)		138
Injury or Sickness Office Visits		
Industrial -first visit	46	
Industrial - return visit	}	
Personal visits	}	568
Total number of people seen at Drexel House		706

Of those seen 46 were referred to University of Chicago Clinics for consultation and one p rson was rejected for employment because of physical findings.

The following table shows the increased use of Drexel House facilities as judged by the total number of visits per month.

Month	Number of visits
August 15 to September 14, 1944	553
September 15 to October 14, 1944	606
October 15 to November 14, 1944	706

000 MLH 1200 Clinical Laboratory Reports- E.K. Marks and L.O. Jacobson, M.D.
October 15 to November 14, 1944

Procedure	Number of examinations performed	Number of abnormal findings
Hemoglobins	696	116
Red counts	584	75
White counts	903	70 below 5000 69 above 10000
Differentials	889	265
Platelets	200	40
Urines	715	184
Retics	60	5
Wassermans	177	0
Misc.	16	0
Sed. rates	181	0
Hematocrits	181	0
Amount of stippling		6
Immature cells		109

Haematological abnormalities (W.B.C. below [illegible] lymphocytes below 1500; reversal of neutrophile - lymphocyte ratio and presence of immature cells

Status of Individual examined	Number examined	Number with abnormalities	Percent
New personnel	66	33	50
Non-exposed personnel	242	72	30
Possibly exposed personnel	713	230	32

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Metallurgical Laboratory

B. CLINICAL MEDICINE AND MEDICAL RESEARCH SECTION

L. O. Jacobson, M. D. , Section Chief

I. The Effect of X-Rays on the Metabolism of Testis 362 MLH 1451 -

E. S. Guzman Barron

The deleterious effect of X-Rays on the formation of spermatozoa is well known. In order to see if this inhibition of spermatozoa formation is related to an inhibition of the metabolibolic activities of the testes, rats were irradiated (whole body radiation) with different doses and the metabolism of testes was measured as oxygen uptake in the absence of added substrate and in the presence of succinate, and as CO_2 output in Ringer-bicarbonate-glucose with $N_2:CO_2$ as gas phase (anaerobic glycolysis). A large number of experiments were performed during the months of June, August, October and November with inconsistent results, except those performed on rats receiving 100r. In Table I data are tabulated of experiments with two series of rats. In general, anaerobic glycolysis was completely unaffected throughout the duration of the experiments, namely 21 days. In many cases there was an increase. The oxidation of succinate (QO_2 succinate) seemed to be unaffected when the O_2 uptake values were calculated subtracting the QO_2 values obtained in the absence of substrate. The QO_2 values (in Ringer-phosphate and no substrate) were definitely lower, except in two instances, one 24 hours after radiation, and the other 20 days after radiation. (Table I).

It may be concluded from these experiments that irradiation with x-ray of the whole body of the rat at a dose of 100r applied in a single dose produces a definite inhibition of the respiration of the testes. The inhibition is not due to succinoxidase inhibition.

Effect of $TO_2(NO_3)_2$ on the Activity of Glucose Oxidase. -- 374 MLH 1403 -- It has been shown previously that TO_2^{++} inhibits the oxidation of glucose by bakers' yeast while it has no effect on the oxidation of glucose by bacteria. This was explained by assuming that glucose was oxidized in yeast through hexosemonophosphate oxidation, since the enzyme for this oxidation was quite sensitive towards $TO_2(NO_3)_2$. Further evidence that the inhibition produced in bakers' yeast is due to inhibition of hexosemonophosphate oxidase and not to direct inhibition of glucose oxidation is given in Table II. The oxidation of glucose by glucose oxidase prepared from liver was unaffected on addition of 0.001 M $TO_2(NO_3)_2$.

Comparison between hydroxy-aspartic acid and citric acid as agents for the treatment of $TO_2(NO_3)_2$ poisoning. 374 MLH 1403. -- The effect of these substances on reactivations after TO_2^{++} inhibition has been tested on two systems: Succinoxidase and the oxidation of glucose by bakers' yeast. The inhibition produced by $TO_2(NO_3)_2$ on succinoxidase was completely released on addition of 20 moles of hydroxy-aspartic per mole of $TO_2(NO_3)_2$. Citric acid produced a reactivation of 75 per cent on addition of more citrate. It may be concluded that in this case hydroxy-aspartic acid is a better releasing agent than citrate. When the test was performed on the oxidation of glucose by bakers' yeast it was found that at a ratio of 10 of releasing agent to 1 of $TO_2(NO_3)_2$ citric acid produced a reactivation of 93 per cent, and hydroxy aspartic acid, 88 percent. (Table III, Figure 1)

Experiments are in progress on the use of both substances in the treatment of TO_2^{++} poisoning in rats.

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TO_2^{++} and proteins. 374 MLH 1401.--It is known that TO_2^{++} combines with proteins. In order to establish the proportion of TO_2^{--} combined with the free portion, ultrafiltration experiments with both dialyzed and undialyzed serum are being performed. To see whether TO_2 is combined with the albumin fraction or with the the globulin fraction, TO_2^{++} was added to human serum protein and after 6 hours dialysis it was separated into its components by electrophoresis in the Tiselius apparatus. The albumin fraction was isolated by the compensating device. It was found that TO_2^{++} was present in both fractions. These studies are in progress.

The appearance of catalase, carbonic anhydrase and phosphatase, in the urine after TO_2^{++} poisoning.-- The Warburg manometric method has been used for the measurement of carbonic anhydrase activity with satisfactory results. Studies are in progress where rabbits are being treated with $TO_2(NO)_2$ and the enzymes above mentioned are measured in the urine. As soon as one of them appears in abnormal concentrations the rabbits will be sacrificed, the blood N.P.N. will be measured and the kidneys will be studied histologically by Dr. Lisco.

Table I

Effect of X-Rays on the Metabolism of Testis (rat)

Q_{O_2} = cmm O_2 uptake per mg dry weight per hr. $Q^{N_2}_{CO_2}$ = cmm CO_2 (or lactic acid) produced per mg Dry wt/hr in Ringer-glucose-bicarbonate and N_2:CO_2 as gas phase.

Radiation	Time after radiation	Q_{O_2}	Q_{O_2} succinate	$Q^{N_2}_{CO_2}$
r	hours			
100	4	1.89	6.41	6.73
		2.65	6.86	8.50
	24	3.52	6.65	8.85
		2.24	6.64	5.81
	48	2.65	7.35	8.27
		2.83	6.94	6.84
	72	2.49	6.85	6.61
		2.76	6.44	6.36
	96	2.56	6.56	6.22
		1.92	5.98	5.47
	120	2.53	7.32	6.96
	15 days	2.31	6.48	6.71
	16 "	2.86	6.43	6.55
	19 "	2.38		6.30
	20 "	3.69	8.81	5.49
	21 "	2.19	6.13	6.63
Normal value		3.28±0.23	7.28±0.3	6.0±0.33

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Table II

Effect of $TO_2(NO_3)_2$ on the Activity of Glucose Oxidase (Liver).

Conditions: 2cc enzyme + 0.15cc of 0.1 per cent DPN (diphosphopyridine nucleotide) + 0.1cc phosphate buffer 1 M pH 7.0 + 0.2cc, 0.2 per cent methylene blue + 0 .4cc 3 M glucose + H_2O to make 4cc. The enzyme was treated with $TO_2(NO_3)_2$ in the absence of phosphate or DPN which were added 10 minutes later. Temp. 38°. Gas phase, air.

TO_2 concentration	O_2 Uptake		Inhibition
	Control	Treated	
M			per cent
0.001	138	151	None

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Table III

Comparison between Hydroxy Aspartic Acid and Citric Acid as Agents for the Treatment of TO_2^{++} Poisoning.

Tested on the oxidation of glucose by bakers yeast. (washed) Buffer, veronal, pH 7.3. $TO_2(NO_3)_2$ was added at about pH 6.5. Ten minutes later the pH was adjusted to 7.3. Temp. 38°. Gas phase, air. Duration of experiments, 60 minutes. Figures give cmm O_2 uptake, blank values subtracted.

System	O_2 Uptake	Inhibition	Reactivation
		percent	percent
Control	331		
$TO_2(NO_3)_2$, $8x10^{-5}$ M	0	complete	
Control + citrate, $8x10^{-4}$ M	330		
$TO_2(NO_3)_2$ followed by citrate, $8x10^{-4}$ M	318	7	93
Control + hydroxy-aspartic acid, $8x10^{-4}$ M	319		
$TO_2(NO_3)_2$ followed by hydroxy-aspartic acid, $8x10^{-4}$ M	279	12	88

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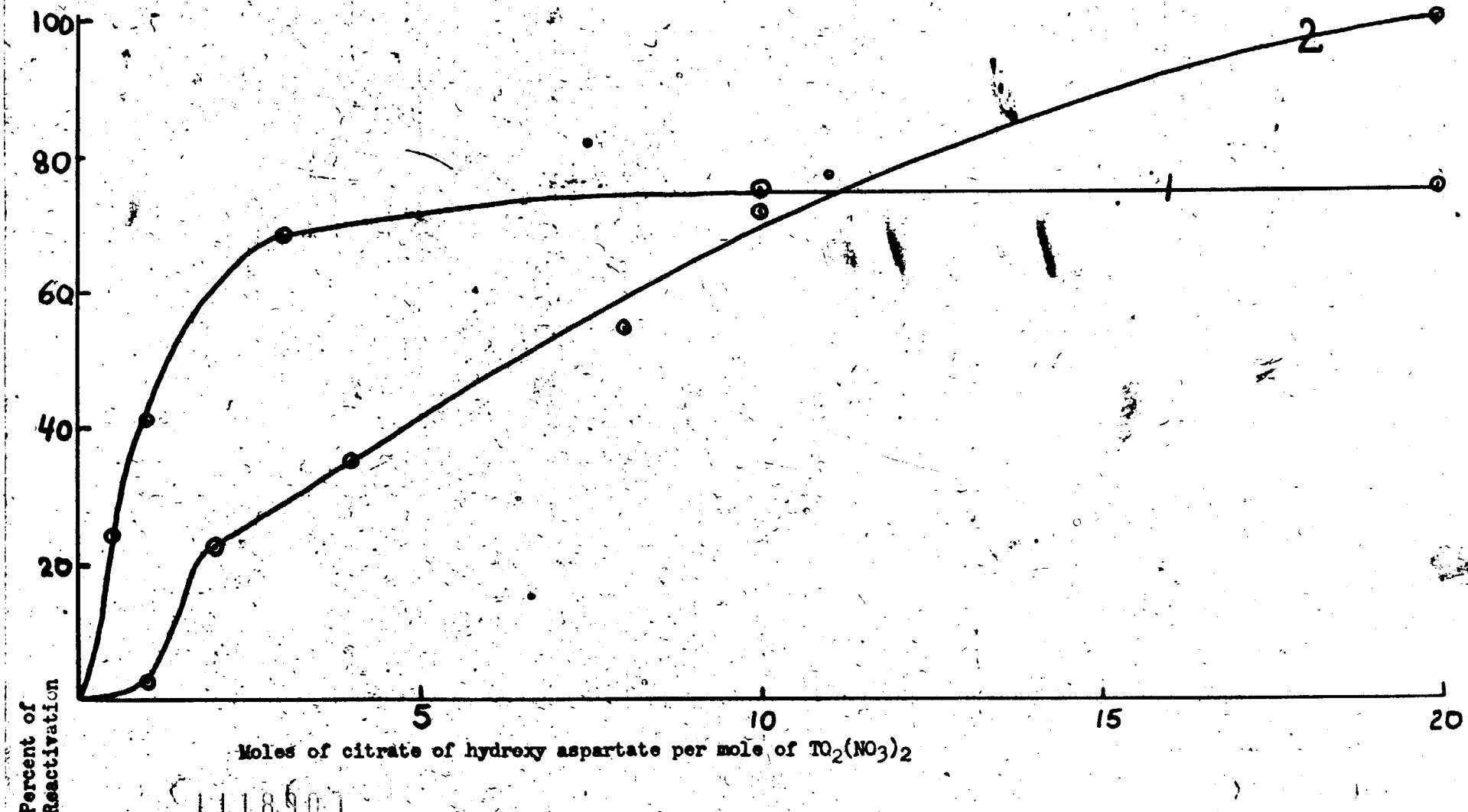
Fig. 1

Effect on the Inhibition of of Succinoxidase Produced by $TO_2(NO_3)_2$



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IV. Clinical Research Group - S. Schwartz

Urine Catalase Excretion 14[illegible] MLH 1325

A final series of studies of urine catalase excretion in Ames personnel has been completed. This study was done because of incomplete data on the group in the October report. It included 13 individuals with the heaviest T exposure and 9 individuals with little or no T exposure. All determinations were done in duplicate or triplicate. A water blank and two urine blanks as described in last month's report were run with every freshly passed specimen. Results agree very well with those described last month, namely there is no significant difference between control and exposed groups.

The data is given in the table below in terms of thiosulfate difference between the blank listed and the incubated urine sample per cc urine. (0.1 cc thiosulfate difference is equivalent to the liberation of 0.011 cc O_2) The iodometric titration procedure used was described in last month's report.

Urine Catalase Activity

Expressed as the difference in cc of 0.01 N thiosulfate needed to titrate the unknown and the 3 blanks respectively per cc of urine.

	Difference obtained using:		
A. Heavy T exposure	H_2O blank	Urine blank No. 1	Urine blank No. 2
1	0.18 cc	0.06 cc	0.06 cc
2	0.08	0.07	0.07
3	0.10	0.08	0.04
4	0.13	0.07	0.06
5	0.07	0.02	0.01
6	0.18	0.10	0.05
7	0.06	0.07	0.07
8	0.15	0.12	0.09
9	0.10	0.00	0.05
10	0.13	0.07	0.05

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A. Heavy T exposure (con't)		H_2O blank	Urine blank No. 1	Urine blank No. 2
11		0.21	0.09	0.09
12		0.17	0.06	0.08
13		0.13	0.06	0.06
	Average	0.13 cc	0.07 cc	0.06 cc

B. Controls				
1		0.12 cc	0.04 cc	0.05 cc
2		0.11	0.06	0.06
3		0.07	0.06	0.04
4		0.12	0.02	0.02
5		0.18	0.08	0.09
6		0.10	0.06	0.05
7		0.13	0.05	0.05
8		0.09	0.11	0.01
9		0.18	0.07	0.05
	Average	0.12 cc	0.06 cc	0.05 cc

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III Medical Industrial Hazard Section

J. J. Nickson, Section Chief

Special Hazard Surveys done at the request of associated agencies (114 MLH 3100)

1. Quality Hardware Company.

   A final report on the health measure was written during the month on the operations formerly carried on at this plant.

2. Revere Copper and Brass, Inc. was visited on October 21, 1944 at the request of the DuPont Company. Details of this visit may be obtained from MUC HG 825. Another visit was made on Nov. 18, 1944. Conditions remain essentially unaltered.

Special Hazard Surveys at the Metallurgical Laboratory (240 MLH 3200)

Inspections have been carried out routinely at the laboratory. Recommendations for correction of health hazards have been made when necessary.

Special Hazard Surveys of associated projects (000 MLH 3250)

The Ames project was visited on October 26, 1944. The visit is reported in MUC HG 826.

Wax Finger Print Impressions (230 MLH 3600)

Total impressions taken during period 10-23 to 11-18-44, 267. 40 impressions were analyzed by Dr. Harvey. 39 were reported as normal, 1 as abnormal.

Capillary Photography Study of Radiation Effects on Skin (373 MLH 3610)

The equipment is still in the experimental stage. No routine analyses have been done with the instrument as yet. The feasibility of infra-red illumination is being investigated. The cooperation received from members of the Physics Division and from members of the Ryerson shop is much appreciated.

Color Photography Study of Radiation Effects on Skin (248 MLH 3620)

Equipment will shortly be used for routine study.

Building and Equipment surveys: beta (241 MLH 3310); gamma (241 MLH 3320)

The two problem assignment numbers will be discussed together. The surveys as done with present instruments do not permit of certain identification of one or the other kind of radiation. The problem is most difficult in the case of the low K. V. gamma rays and the high enery beta rays.

In general the activities are soft gamma rays or beta rays. Shielding for total body radiation does not present a problem. Exposure of the hands is more difficult to control.

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New Chemistry: A new system of reporting unsatisfactory conditions to the supervisors has resulted in much more prompt clean-up of such conditions. As a result the activity found in various rooms is much reduced. The levels of activity found have in no case markedly exceeded tolerance.

Site B: The tuballoy and TX contamination problem has been partially solved by the installation of filters in the exhaust line from the burnout furnace. Smear surveys of contamination in the rooms continue to show widespread activity. The degree of contamination has dropped somewhat.

Site B Annex: Numerous areas of low level activity are frequently found. Clean up, when possible, is prompt. One spill involving 80 micrograms of radium occurred. Clean up was prompt and adequate.

West Stands: The Semi-works rooms have shown some lessening of contamination in work areas during the past month. The second floor laboratories have in general shown wide spread contamination with small amounts of activity, mostly beta. Room 217, the hot lab has also shown greater than tolerance levels for gamma radiation during work with Clinton slugs.

Armory: Surveys of special materials vaults have only occasionally shown greater than tolerance radiation. In every instance corrective measures have been promptly applied.

Building and Equipment Surveys, Neutron Radiation (241 MLH 3330)

No routine surveys are being done at this time. No suitable instrument is is available. Mr. Simpson of the Instrument Section is at present working on a design of an instrument for measuring slow neutrons.

Personnel Surveys: Beta (214 MLH 3340); Gamma (214 MLH 3360)

a) Hand surveys are done with G-M counter installations. Routine hand counts are taken at West Stands, Site B Annex and New Chemistry. The number of hands with greater than tolerance contamination is low.

b) Badge meter surveys. 450-500 films are developed each week. During the past month only one metallurgical laboratory employee had a reading greater than 0.6 r for the week. It was 0.85 in the window space. The total of the pocket meter readings for the week were 0.05. He works in West Stands. His laboratory studies are normal.

c) Pocket meter surveys. 99 pocket meteres gave readings of greater than 0.1 r for one day during the month ending November 11, 1944, but as noted above only one man exceeded the total weekly tolerance. 63 of these were felt to be valid readings. The break down by sections is as follows:

Section	Separate Readings
Cole	44
Nickson	6
Seaborg	5
Semi-works	4

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Feld	2
Site B Maintainance	1
Sugarman	1
	63

The high number of readings from the Biological Section of the Health Division reflects, in part at least, the recent increase in the amount of active material being handled. Among these exposed however are the maintainance workers in the animal farm. It is entirely possible that some of the readings listed above may actually be due to rough handling.

The plan recently adopted at Clinton for checking high pocket meter readings against the reading on the film by developing the film of the day the high pocket meter reading is found will be inaugurated here in the near future.

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IV. BIOLOGICAL RESEARCH SECTION

K. S. Cole, Section Chief

A. RADIOACTIVE MATERIALS - MAMMALS

1. Development of Aerosol Exposure Methods (244 MLH 2101)

Ether atomizer. A possible method of producing an aerosol without introducing excessive amounts of diluting air is a force feed atomizer where an either solution is forced through a small orifice into a high velocity air stream. The ether vapors are taken up by a bed of active carbon. To date the yields have been small as most of the material is lost in the carbon or by impingement on the walls.

Combusted Spray. Another method of dispersal was that of burning in oxygen the fine droplets of a solution of organic complex atomized in an inflammable organic solvent. The solution was fed slowly by means of a 1/4 cc hypodermic syringe in to a high velocity oxygen stream (1 l/min through an 0.013 "orifice"). Just past the entrance point a continual high voltage spark discharge ignited the atomized solution. Combustion was complete in a non-luminous flame and no carbon particles were observed. The chief disadvantage of the method lies in the violent thermal impingement to which the resultant particles are subjected. When the combustion was run in a 2" diameter cylinder 100% of the activity was on the cylinder wall. When a .2 l balloon flask was used 3% of the total activity could be detected as aerosol; with a 0.5 l balloon flask up to 17.5% of the total activity was in the air., and at least twice this much was on the walls of the flask. Electron micrographs of samples collected with the thermal precipitator show irregularly shaped particles all under 0.5μ in diameter.

Exposure chamber. A static exposure chamber has been constructed and tested. It consists of a small stainless steel chamber from which 28 rats breathe through tubes inserted into their tracheae. The rats lie on shelves which are firmly fixed to the side walls. The entire unit of wall plus shelves can be removed from the chamber by releasing two clamps. Aerosols are introduced through ports in the front face. Aerosol samples are withdrawn through a thermal precipitator mounted in the lucite top. The chamber operates by filling it with oxygen just before putting up the aerosol. Then air is slowly sucked in to replace the O_2 consumed by the rats. A test run carried out with tracer Ce is described below.

2. Inhalation of 300 day Cerium. 244 MLH 2134

A tracer run was carried out using the chamber described above. Onemc of radioactive Ce was placed on a carbon electrode. An arc was struck just inside the front face of the chamber (atmosphere-oxygen) for 35 sec. Dust samples were taken periodically with the thermal precipitator and gas samples for O_2 analysis. All the activity came off the electrodes but only 18 percent was dispersed as an aerosol. This disappeared from the air with a half life of 13 min.

Analytical data on distribution are not yet available but we can get a figure for retention of a carbon arc smoke. The exponential disappearance of activity from the chamber atmosphere makes it possible to set up the following relation:

$$R = \frac{V \lambda m}{v X_o (1-e^{-\lambda t}}$$

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R = fraction of inhaled activity which is retained.
V = chamber volume (ml)
w = units of activity deposited in lung (gm)
$\lambda = \frac{\ln 2}{\text{aerosol half-life}}$
v = rat ventilation rate (ml/min)
X_o = units of activity in chamber atmosphere
t = time of exposure (min)

Preliminary counts on wet tissues indicate retention to be of the order of 5 percent.

3. Inhalation of 57 day Yttrium 244 MLH 2135

Tracer data are now available on Y for 30 days after administration as an atomized solution of the chloride. The activity leaves the lung very rapidly at first (70 percent is gone within one-half day) and then slows down to an average half-life for the remainder of about 7 days. Of the activity leaving the lung, 12 percent finds its way to the skeleton and the rest is excreted, predominately in the feces.

4. Acute Radio-Toxicity of Yttrium from Fission by Injection in Rats. 246 MLH 2216a

Radio-yttrium (largely Y^{92}) as YCl_3 was injected into the heart of white rats. Five animals each received 1, 3, 5, 7, or 10 μc per gram of body weight. All five of the 1 μc/gm and one of the 3 μc/gm animals are alive on the twentieth day. For the other groups the average days to death are 6.7, 10 μc/gm; 8.0, 7 μc/gm and 10.5, 3 μc/gm (4 animals). On autopsy hemorrhages were found in the gastro-intestinal tract and sometimes in the lungs. The probable mid-lethal dose is below 2 μc/gm of body weight. Y^{92} is, therefore, more toxic than Sr^{89}, Ba^{140} and Zr^{93}-Cb^{93} for which the mid-lethal doses for rats are 4 to 5 μc/gm.

5a. Acute Radio Toxicity of Zirconium - Columbium by Injection. 246 MLH 2213a

Distribution in Rats

As reported last month rats were injected intracardially with toxic amounts of solutions containing 50 percent Zr^{93} and 50 percent Cb^{93}. Most of the tissue and excreta samples examined retained this 50-50 relationship, approximately. Exceptions to this are muscle which contained about 35 percent Zr and 65 percent Cb, and urine which contained 25 percent Zr and 75 percent Cb. Because of glassware contamination and a net deficit of zirconium these studies are being repeated under more stringent conditions.

5b. Analysis of Zr^{93}-Cb^{93} Mixtures. 246 MLH 2201

The standard practice of separating radiations of different types and energies by means of their Al absorption curves is being adopted to supplement or replace chemical analysis under certain conditions.

Zr - Cb mixtures:

The relative percentages of Zr and Cb in a solution containing only these two radio-elements can be readily determined from two points on the absorption

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curve. The weak Cb betas are completely cut out by 30 mg/cm^2 Al, whereas the stronger Zr betas are not. All betas are cut out by about 100 mg/cm^2 Al, whereas the gamma rays are not materially affected. Therefore, the following relations hold:

1) $R35 = Zr_\beta + Zr_\gamma + Cb_\gamma$

Where R35 is the activity measured through 35 mg/cm^2 Al absorber, and Zr_β, Zr_γ and Cb_γ are the radiations coming through this absorber.

2) $R550 = Zr_\gamma + Cb_\gamma$

Where the symbols are as in (1). Since the γ absorption curve has practically zero slope between 35 and 550 mg/cm^2 Al, the gamma components and essentially the same through each absorber.

At any particular set of conditions, the Zr_β is associated with as certain γ readings, and the ratio (F) of beta to gamma radiation can be determined from the absorption curve of freshly purified Zr.

Therefore,

3) $Zr_\beta = R35 - R550 = (Zr_\beta + Zr_\gamma + Cb_\gamma) - (Zr_\gamma + Cb_\gamma)$

4) $Zr_\gamma = FZr_\beta$ where $F = \frac{Zr_\gamma}{Zr_\beta}$ at R35

F varies with each instrument but remains constant for a particular instrument for a long time.

5) $\text{percent Zr} = \frac{F\,(R35 - R550)}{R550} \times 100 = \frac{Zr_\gamma}{Zr_\gamma + Cb_\gamma} \times 100$

$\text{percent Cb} = \frac{R550 - F(R35 - R550)}{R550} \times 100 = \frac{Cb_\gamma}{Zr_\gamma + Cb_\gamma} \times 100$

Within the limits of the accuracy to which the Zr_β measurement can be extrapolated to the amount of Zr beta radiation at the corresponding values in microcuries can be determined.

The method was checked with known mixtures of the two isotopes between the ranges of 10% to 90% Zr in the mixture. The error is less than 5% in the middle ranges, and less than 10% at the 2 extremes. The method was developed to permit a rapid analysis of animal tissues for differential distribution after injection of Zr - Cb.

$$\%Zr = \frac{Zr_\gamma}{Zr_\gamma + Cb_\gamma} \cdot 100$$

$$\%Cb = \frac{Cb_\gamma}{Zr_\gamma + Cb_\gamma} \cdot 100$$

5c. <u>Removal of Oxalic acid from Zr - Cb Solution.</u> 246 MLH 2201

Carrier-free Zr^{93} - Cb^{93} solutions are complexed with oxalic acid as the last step in the preparation at Clinton. They are shipped and stored in this form

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to prevent adsorption of the isotopes onto the walls of the containers. The amount of oxalic acid used would be toxic if injected to animals. Therefore, the oxalic acid must be eliminated or markedly reduced shortly before administration to the experimental animals.

One method is to evaporate the solution and take the residue up in 10 ml of conc. nitric acid. The nitric acid is kept at 90°C and 30 percent hydrogen peroxide is added, one drop per minute for six minutes. The solution is evaporated to dryness and the residue is dissolved in water or saline. The solution usually contains less than 0.02 percent oxalic acid and 86-96 percent of the radioactive isotopes.

Sublimation of the dry residue appears very promising. Results with tracers show that sublimation in procelain at 200°C removes the oxalic acid quantitatively without baking the active material into the container and without smoking off the active isotopes. Extraction with 0.1 percent oxalic acid yields 100 percent recovery; 0.01 percent oxalic acid yields 96 percent; water alone yields 86 percent. Sublimation apparatus will be constructed for the "rat room".

6a. Acute effects of Sr^{89} on the Peripheral Blood of Mammals. 246 MLH 2421

No appreciable effect on the hemoglobin was noted through 114 days in rats given Sr^{89} intraperitoneally at 0.25, 0.62 and 2.5 μc/gm. An abrupt and significant fall in the lymphocyte and heterophil counts occurred at all levels by 4 days. The number of heterophils returned to the normal range in the rats treated with the two smaller doses by 7 days and fluctuated in the lower portion of the normal range below the mean of the control animals. The heterophil count remained markedly low for 37 days in those treated with the largest amount and thereafter gradually increased; at 114 days it was equal to those of the next lower dose. The lymphocytes reacted in a similar manner except that the depression occurring initially was largely maintained through the last sampling at 114 days.

Strontium 89 given by stomach tube in doses of 5 μc/gm of rat had an effect on the number of heterophils per mm^3 roughly equivalent to 2.5 μc/gm given intraperitoneally. A dose of 2.5 μc/gm I.P. had a greater depressant effect on the lymphocytes.

6b. Chronic Toxicity of Radioactive Strontium. 246 MLH 2721a

Pilot experiments with Sr^{89} have shown a significant incidence of lymphoma within 7 months after the first injection. This is almost as striking after a single dose of 2.5 μc/gm as it is after doses repeated at monthly intervals to re-establish the 2.5 μc/gm amount.

7. The effects of Acutely Administered Fission Mixture on the Peripheral Blood of Mammals 246 MLH 2420

Fission mixture given by stomach tube to rats in doses of 1.7, 7.0 and 27 c/gm respectively produced a decrease in the number of lymphocytes per mm^3, apparent by 72 hours. With the lowest dose (1.7 μc/gm) this effect was transitory with a return to the normal range between 7 and 14 days. After 7 μc/gm the number of lymphocytes per mm^3 had returned to the normal range only after 35 days. A continuous fall occurred in the number of lymphocytes after 27 μc/gm until death precluded further sampling (21 days).

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The heterophils were decreased in number only by the two higher dose levels. This decrease in count was not appreciable until after 14 days with 1.7 μc/gm and after 7 days with 27 μc/gm.

B. EXTERNAL RADIATION - MAMMALS

1 Effects of Multiple Doses of X-Ray on Mammals. 142 MLH 2330

Two surviving rats receiving 12.5 r per day have now accumulated approximately 3662 r. Mice are being exposed to 20 r per day and 40 r per day.

2 Biometric and Statistical Analysis of Survival Data 142 MLH 2370

Mortality data for rats at 400, 500, 600, and 700 r and rabbits at 800 r and 1000 r have been analysed by methods described in past reports. The rate of death at a given time is a measure of the morbidity at that time. The early killing (less than 48 hours) does not fit into this picture but proceeds from no killing at and below 700 r to 25 percent for 1200 r and higher doses. Rat morbidity functions have two components which have different dose dependences and are present to different degrees in the two sexes.

Deaths were tabulated for ABC and CF1 mice for a period of 210 days post-irradiation. Mortality in control females of both strains is about 0.7 percent per month. ABC control males have about the same death rate as the Fe males while CF1 control males have a significantly higher death rate. Tabulation of irradiated animals begins 30 days after irradiation. Mortality of irradiated CF1 of both sexes is considerably greater than control levels.

3 Histological Effects in Mammals of Single Exposures to X-rays. 142 MLH 2510

Sacrifice of additional rabbits following 800 r with particular reference to the difference between "survivors" and dead or moribund animals yielded the following additional information:

1. With the exception of the ovary, histological structure may be nearly within normal limits in survivors at 21 days. Extra-medullary blood cell formation and increased numbers of plasma cells and pigment-filled macrophages were about all that distinguished "surviving" rabbits from the controls at this period.

2. The ovary was depleted of all but the most immature follicles by 11 days and no mature follicles were seen thereafter.

3. The testis showed degeneration of spermatogonia only in the early hours but at 9-14 days the germinal epithelium was reduced to about 15 percent of normal. In rabbits examined at later times the testis was normal in appearance.

4. The histological picture in those animals which died or were moribund at sacrifice in the 9-14 day period was essentially similar to that seen in apparent survivors in this period. However, the dead or moribund animals examined at subsequent intervals (21, 35 and 37 days) all showed a histological picture similar to that seen at 9-14 days. This was most strikingly demonstrated in the severely depleted bone marrow at these late intervals. Survivors at these intervals were essentially normal in appearance.

4. Effects of Single and Multiple Doses of X-Rays on Mammals. 142 MLH 2310 and 2330

X-ray in sublethal single and divided doses produced a significant incidence of mammary carcinoma noted 8 months after beginning of treatment in a strain of rats which does not ordinarily develop this tumor at this period of life.

5. Effects of Single Exposures to Fast Neutrons upon the Peripheral Blood of Rabbits. 142 MLH 2413

The effects of neutrons produced in a cyclotron operating at 8 deuterons in doses of 70-79 n, 83-95 n, 100-108 n and 128 - 142 n upon the peripheral blood picture of rabbits is given in figures 1-3. Doses of 70 n or above produced an initial rise in the number of heterophils (Figure 1) apparent by 3 hours but more striking at 24 hours. Thereafter, a decrease in level occured, the lowest level occurring between 72 and 96 hours. No significant difference in the level of depression was apparent with these doses. Only between 168 and 216 hours was a questionably significant difference seen in the number of the heterophils of the four dose levels. A precipitous fall in the number of lymphocytes (Figure 2) occured by 3 hours; a further fall was apparent at the 24 hours interval and there was little significant recovery by 216 hours. No significant difference existed in the level of depression reached by any of the doses. The effects of lower doses of cyclotron neutrons upon the peripheral blood of rabbits are shown in figures 4-6. The three lower dose levels (8-10 n, 26-28 n, 52-66 n) caused a rise in the number of heterophils (Figure 4) at 3 hours much like that reported above for the higher dose levels. This rise persisted at 24 hours in the rabbits treated with 26-28 n and 70-79 n, but returned to the normal range in all at the 48 hour interval. Thereafter, a depression of the heterophil level occured which is roughly proportional to the dose. By 168 hours a return to the normal range is apparent in all these lower dose levels. The number of lymphocytes (Figure 5) dropped precipitously by 3 hours. This drop continued through 24 to 48 hours with all dose levels. By 216 hours the number of lymphocytes per mm^3 had returned to the normal range in the series which received the lowest dose (8-10 n) but not in the others. As was true of the heterophils, distinct levels of depression of the number of lymphocytes are apparently proportional to the dose delivered.

An X/N analysis will be presented next month.

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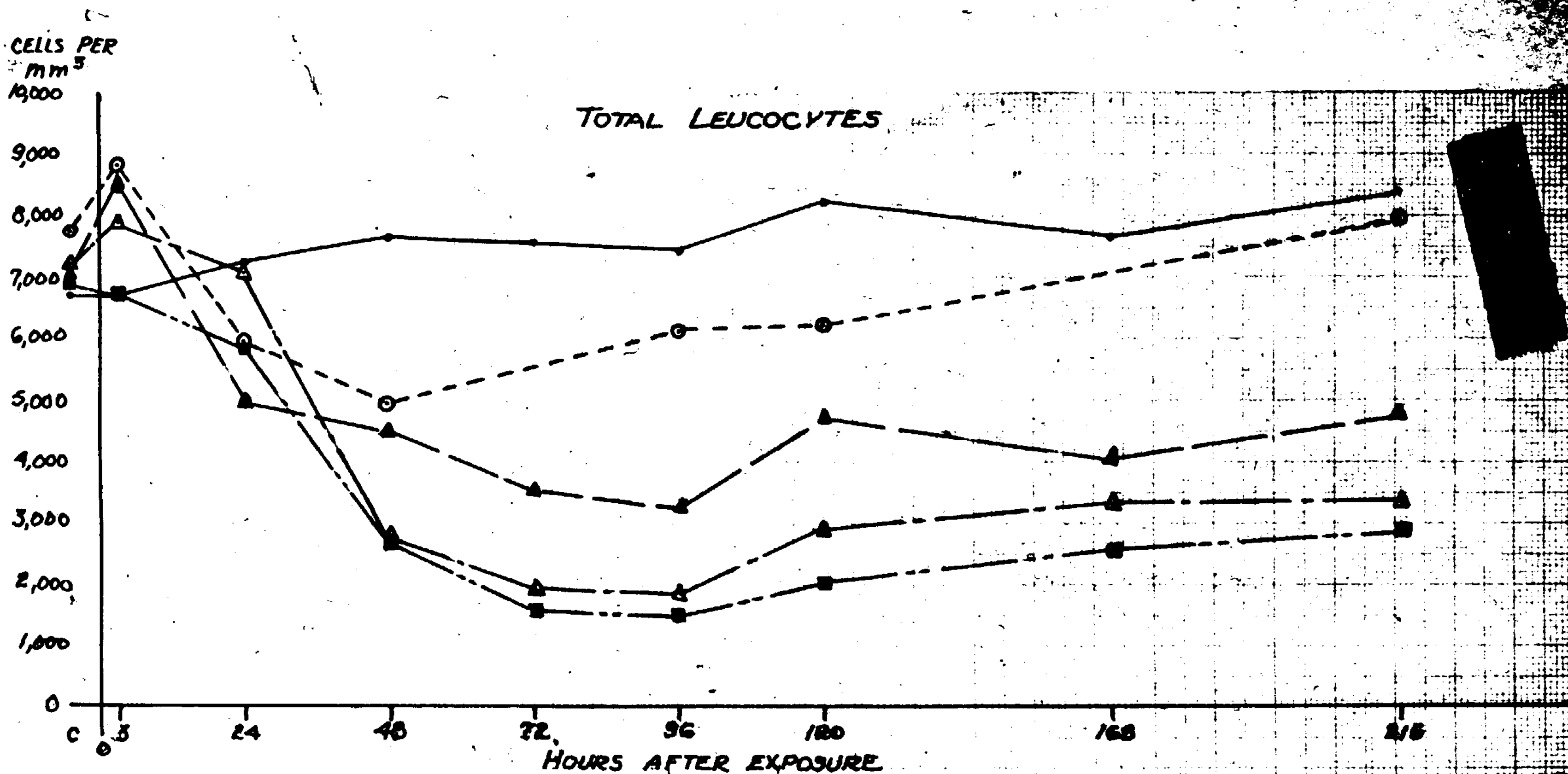

Dose	NUMBER OF RABBITS									KEY
Control	14	13	17	16	9	11	13	17	18	Control
8-10n	4	4	4	4		4	4		4	8-10n
26-28n	6	6	6	6	4	2	3	6	5	26-28n
52-66n	9	11	11	11	2	11	2	10	10	52-66n
72-79n	15	17	17	14	11	10	9	15	15	72-79n

FIGURE 6: RABBITS: TOTAL LEUCOCYTES AFTER SINGLE DOSES OF FAST NEUTRONS 8n - 79n

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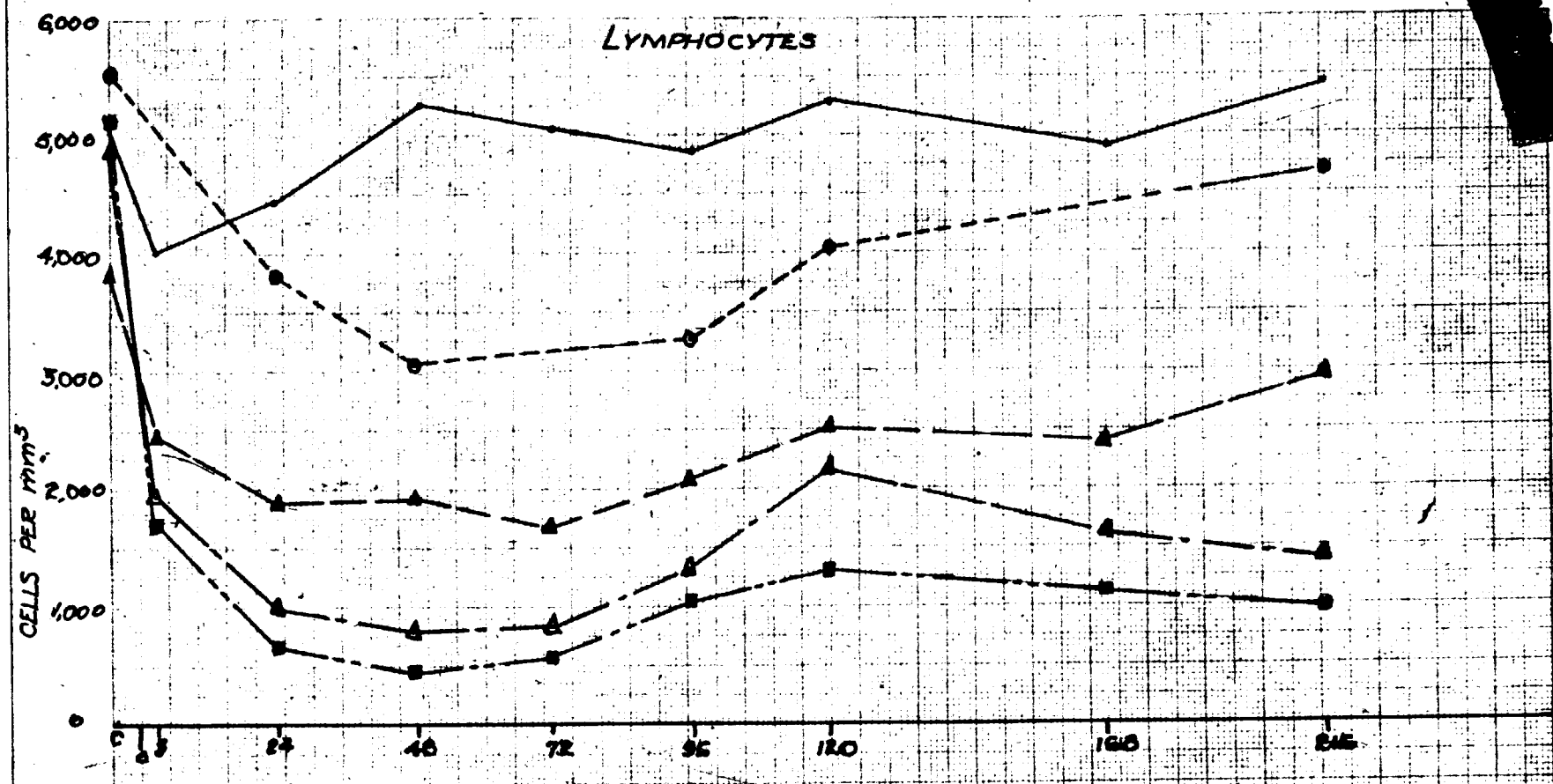

Dose	Number of Animals								
Controls	14	13	17	16	9	11	13	12	12
8-10n	4	4	4	4		4	4		4
26-28n	6	6	6	6	4	2	5	6	5
52-60n	9	11	11	11	2	11	5	10	10
70-79n	15	17	17	14	10	10	9	7	14

Key
- Controls
- 8-10n
- 26-28n
- 52-60n
- 70-79n

FIGURE 5: RABBITS: LYMPHOCYTES AFTER SINGLE DOSES OF FAST NEUTRONS

8n - 79n

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E. ASSOCIATED PROJECTS

I. N. C. I.

R. S. Spencer, Chief

BIOLOGICAL ACTION OF X AND GAMMA RAYS

E. Lorenz, J. E. Heston, M. K. Deringer, A. Eschenbrenner

I. Continuous exposure for 8 hours daily

Daily dose: 8r, 4r, 2r, and 0.1r.

Approximate 'total' doses up to date of mice and guinea pigs (with the exception of the original guinea pigs of the 8r per 8 hours level which are all dead) 5000r, 2500r, 1250r, 625r and 66r (acute exposures of 12.5r and 50r not added). Start of this experiment February to March 1943.

Approximate total doses of rabits: 4100r, 2050r, 1025r, 512r and 50r (acute exposures of 12.5r and 50r not added). Start of this experiment July, 1943.

Approximate total dose of inbred guinea pigs (family 13) exposed on the 8r per 8 hours level 1650r. Start of this experiment May, 1944.

Approximate total dose of hybrid guinea pigs of the term experiment exposed on the 8r per 8 hours level 650r. Start of this experiment August, 1944.

Approximate total dose of Strain A mice exposed on the 8r per 8 hours level 1600r and Strain A mice of the same level used for blood counts 1550r. Start of this experiment May, 1944.

Mice: Since the last report 5 mice died and 17 were killed. Gross diagnosis at autopsy gave the following findings: Of the 5 that died cause of death was more or less obscure. 2 had severe eczemas and in 3 the blood picture indicated an infection. Of the 17 that were killed either on account of palpable tumors or severe sudden loss of weight, 12 showed at autopsy grossly malignant lymphomas, the remainder showed various lesions not connected with the irradiation. The distribution of the malignant lymphomas amont the different levels is as follows: 1 control mouse (21 months old); one mouse which had been irradiated with 12.5r given in 5 hours at the age of approximately 4 months (age at death 23 months); two mice of the 0.1r level (approximate total dose 65r), one of which had received in addition 12.5r given in 5 hours at the age of approximately 4 months (age at death 23 months); one mouse of the 1r per 8 hours level (approximate total dose 600r) which had received in addition 12.5r given in 5 hours at the age of approximately 4 months (age at death 21 months); two mice of the 2r per 8 hours level (approximate total dose 1200 and 1250r) both of which had received in addition 12.5r given in 5 hours at the age of approximately 4 months (age at death 21½ and 22½ monts); one mouse of the 4r per 8 hours level (approximate total dose 2500r) which had received in addition 12.5r given in 5 hours at the age of approximately 4 months (age at death 22½ months); two mice of the 8r per 8 hours level (total doses approximately 4800 and 5000r) one of which had received in addition 12.5r given in 5 hours at the age of approximately 4 months; one mouse that had received 300r on the 8r per 8 hours level at the age of 2-3 months (age at death 22 months); and one mouse that had received 600r on the 8r per 8 hours level at the age of 2 to 4 months (age at death 23 months).

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Up to the present the total number of mice with malignant lymphomas

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is 58.

They are distributed among the different levels as follows (see table in last month's report)

Controls:		4 mice
Acute exposure only	(12.5r (5 hours)	2 mice
	(50r (5 hours)	1 mouse
0.1r per 8 hours per day		3 mice
1r per 8 hours per day		3 mice
2r per 8 hours per day		9 mice
4r per 8 hours per day		9 mice
8r per 8 hours per day		22 mice
8r per 8 hours per day (exposure limited to 300r)		3 mice
8r per 8 hours per day (exposure limited to 600r)		2 mice

Again, as stated last month, only a few of the malignant lymphomas of the 2r and 4r and the majority of those of the 8r per 8 hours level (receiving uninterrupted exposure) are considered due to the irradiation.

During the last months the number of mice found at autopsy with ovarian tumors has increased considerably. A table of these findings will be given in the near future.

Guinea Pigs: During the month one guinea pigs of family 13 (on the 8r per 8 hours level) died on account of intra-abdominal hemorrhage, 3 were killed in moribund condition on account of aplastic anemia. The lethal dose of these guinea pigs was approximately 1600r. It may be recalled that the lethal dose for hybrid guinea pigs ranged from 600 to 4000r, while that for the inbred strain of family 2 ranged from 1200 to 1600r. It seems that also the range of the lethal dose of the inbred guinea pigs of family 13 will be narrow but somewhat higher than the lethal dose of the guinea pigs of family 2. The lethal doses for the inbred guinea pigs corresponds roughly to the range in which most of the hybrid guinea pigs died. The gross picture at autopsy of these guinea pigs was identical with that found in all guinea pigs autopsied on account of aplastic anemia, hemorrhagic lymph nodes, ecchymoses of upper small intestine and wall of stomach, etc.

The term experiment, in which hybrid guinea pigs were exposed to 3r per 8 hours daily until the first case of aplastic anemia began to appear, was finished during the month. 6 male and 6 female experimental guinea pigs were exposed with the same number of controls. 1 male and 1 female each of experimental and control guinea pigs were killed and autopsied after having received a total dose of approximately 350r. The experimental guinea pigs were replaced at this time. All remaining guinea pigs and controls were killed during the month after 2 animals had developed aplastic anemia (total dose of approximately 650r). Also the 2 animals that were replaced after a total dose of approximately 300r were killed. All tissues are in Chicago with the exception of those of one experimental animal which showed grossly an ovarian tumor at autopsy not as yet proven neoplastic by sections.

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One guinea pig. exposed on the 4r per 8 hour level (total dose approximately 2400r) developed aplastic anemia and was autopsied.

Rabbits: The rabbits are also alive.

II. Breeding experiments

Nothing new to report.

III. Hematology

Mice; The blood picture of the control and experimental mice is approximately the same as that reported last month. However, the number of mice, especially male mice showing high total white counts with differential counts either normal or showing a high percent neutrophil count is increasing. Three animals of the same box in which most of the mice showed high total white counts, died suddenly at the same time with cause of death not apparent. It is assumed, therefore, that these high counts are due to an infection of unknown origin. On the whole, however, these animals do not appear ill. They show normal activity and fairly constant weight.

As pointed out previously, about 50% of the animals showing malignant lymphoma have typical white counts up to 200,000. The other 50% have a more or less normal blood picture. Lately a number of the leukemic mice showed ascites at autopsy. A smear of the (turpid) ascitic fluid of one animal showed the presence of lymphocytes.

The red count, platelet count and hemoglobin content are within the limits of the controls for the animals of the 0.1r, 1r and 2r per 8 hours levels, while there is some lowering of these counts in some of the animals of the 4r per 8 hours level (total dose approximately 2500r). Two of the 3 surviving animals of the 8r per 8 hours level (total dose approximately 5000r) have considerably lowered red and pletelet counts and hemoglobin, while in one the blood picture is approximately normal. The mice of the 8r per 8 hours which were removed after having receiving doses of 300r and 600r, show approximately normal counts.

The Strain A mice, exposed on the 8r per 8 hours level (approximate dose 1550r) show an average total white count of approximately 3500, while the average total white count of the control is approximately 8000.

Guinea Pigs: The blood picture of the hybrid guinea pigs exposed since the beginning of last year on the 0.1r and 1r per 8 hours levels as well as those given acute exposures only is essentially normal as compared to the controls. Some of the animals of the 2r per 8 hours level (total dose approximately 1250r) show all counts lowered. All surviving animals of the 4r per 8 hours level (total dose approximately 2400r) show lowered counts in varying degrees with the platelet and red counts most affected. One animal was killed on account of aplastic anemia. The animals of family 13 on the 8r per 8 hours level show all counts lowered in varying degrees with the platelet count most affected. Four animals developed anemia and were killed during the month (total dose approximately 1600r)

The hybrid guinea pig exposed on the 8r per 8 hours level (terminal dose approximately 650) showed counts on the day of autopsy which ranged from approximately normal to extreme lowering of all counts.

There is no change in the blood picture of the rabbits from that reported previously. (lymphopenia with increasing total dose).

IV. Pathology

Guinea Pigs: There are no additional sections for histological examination since last report.

Mice; Tissues from five mice are available for histological examination since the last report.

Two of these were male mice who had been exposed on the 8r per 8 hours level (total dose approximately 4500r). There was extreme atrophy of the testes but in each animal a few spermatogenic elements could be seen. One of these had a malignant lymphoma with involvement of lymph nodes, spleen, liver, thymus and lung. The other had pyelonephritis with associated amyloid disease of the liver and spleen which is considered to be unrelated to the experimental procedure.

One female mouse had been exposed on the 4r per 8 hours level (total dose approximately 2250r). Ovaries were small, devoid of follicles and there was moderate invaginative downgrowth of surface germinal epithelium. This and the two mice described above had several lung tumors which are of a type commonly seen in untreated animals of this strain.

One male mouse had been exposed on the 8r per 8 hours level for approximately 1 month at the age of 2-3 months (total dose 300r). Lymph nodes contained giant germinal centers and the Malphighian bodies of the spleen were large and numerous. In these structures of both organs there were small foci of necrotic debris and scattered mitoses. Other organs, including testes, were normal.

One male mouse had been exposed on the 2r per 8 hours level (total dose approximately 1100r). This animal was found dead and advanced autolysis had occurred but sections of intestinal nodules showed sufficient detail on histological examination to leave no doubt of these being invasive lymphomas.

In all these animals there was no bone marrow atrophy.

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E. ASSOCIATED PROJECTS

II. U. OF C. RADIATION LABORATORY

J. G. Hamilton and Associates

Technical Progress Report on Metabolic Studies of Fission Products

1. Radio-Autographic Studies

The preparation of radio-autographs from lungs of animals exposed to inhalation of U_3O_8 smokes containing fission products are being continued. It is anticipated within the next several weeks we will have available radio-autographs from the lungs of animals 64 days after exposure to the radioactive smoke.

2. Soil Studies

The assay of the algae from X-10 was completed. The activity was about 5.8μc per gram dry weight. For an equivalent filter thickness of 8 mgm/cm^2, the radioactive composition was as follows: Cs, 2.44%; Ba+Sr, 3.83%; Y, 3.03%; Ce, 30.2%; Zr+Cb, 50.7%; Ru+Te, 9.74%. Results of the assays of the algae strongly suggest that the active material was fixed on the surfaces of the cells rather than incorporated into the living tissue of the plant.

Additional studies were made on the uptake of activity by barley plants from clay suspensions. An assay of the leaves of those plants grown in Y and Ce solutions showed the activity to be due to element in questions and not due to impurities. A study of the uptake of Y by barley plants as a function of the clay content of the culture medium was carried out. An inverse relationship was established between the clay content and the activity on the roots. Experiments showed that the activity on the roots was not due to the adhesion of clay particles to the root surfaces.

Plants were grown in active culture solutions in the absence of clay. For each element (Y, Cr, Zr+Cb, Sr) the total activity on the plant was comparable with those grown in clay suspensions. However, for Y, Cr, Zr+Cb, less of the element was accumulated in the tops. The behavior of Sr was relatively unaffected.

Radio-autographs have been set up to determine the nature of the fixation process in the roots, i.e. absorption or adsorption.

Clay fractions from a variety of soil types have been isolated. Fixation studies on these fractions will be started shortly.

3. Tracer Smoke Studies

The long term experiments, namely 64 day and 128 day intervals after exposure, are not as yet available but will be presented shortly after sacrifice of these groups. A much larger exposure chamber has been completed by Mr. Scott and will be put into operation within the next few days. This development makes it possible to expose thirty rats at one time to various types of smoke and dusts. Its initial use will be for the exposure of rats to fission product smokes produced by the volatilization of these substances in the form of their chlorids and free from uranium.

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4. Projected Studies for the Next Two Months.

The soil, plant, smoke and radio-autographic studies will be continued.

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E. ASSOCIATED PROJECTS

III. MICHAEL REESE HOSPITAL

A. Tannenbaum

Subacute effects of ingestion of large amounts of T nitrate. It has been reported (CH 2446) that the response of mice to the feeding of $T_2(NO_3)_2$ is dependent on the dosage. Mice which were fed 10 mg of T as the nitrate in the daily ration showed no evidence of T intoxication at any time during an experiment which lasted for about 1 year. Mice which received 20 mg of T (about 1% T nitrate in the diet) developed an acute intoxication during the first 3 weeks. During the first 2 weeks, the mice failed to grow or lost weight, and consumed less food and water. The most striking pathological change was a severe cloudy swelling or an acute necrotizing nephrosis. A few mice died during this acute stage. The animals which survived recovered more or less completely and even after a year on the diet containing the nitrate showed no signs of toxicity or significant pathological change except that they weighed about 15% less than the control mice.

When mice were fed 80 mg of T as the nitrate in the daily ration (about 4% of the diet) a similar but more severe acute intoxication resulted. During the first two weeks the mice lost from 25 to 30% of their initial weight, and 9 of 20 mice died. Then, in contrast to the recovery observed in mice that had received 20 mg of T, the mice that received 80 mg of T daily showed the following course: after the initial weight loss to about 16 gms the average weight of the animals stabilized at this low level until the 43rd day; no deaths occurred between the 12th day (approximately the height of the acute stage) and the 43rd day; food and water consumption was near normal during this period. Beginning at about the 43rd day, the mice began to eat less food (about 1.5 gm in comparison with normal intake of about 3.2 gm) and lost weight gradually; among 8 C57 Black mice, 4 deaths occurred (45, 51, 53, and 60th day). The remaining four mice lost 4 to 5 gms in the interval between the 43rd and 64th day of the experiment at which time they were sacrificed for study of gross and microscopic pathological changes.

C57 Black mice which had been ingesting 80 mg of T as TO_4 or $Na_2T_2O_7$ for 43 days were transferred to the diet containing 80 mg of T as the nitrate. No deaths had occurred among these mice while they were receiving the TO_4 or $Na_2T_2O_7$, and by the 43rd day they had regained the weight lost during the first two weeks. After being transferred to the T nitrate diet, these mice maintained their weight for about2 weeks and then began to decline. During the next three weeks they consumed less food and lost from 3 to 6 gms at this time, they were sacrificed for gross and microscopic study. The findings were qualitatively similar to those observed in the mice which had received the T nitrate throughout the experiment and are therefore discussed together with the latter.

Pathological changes: The mice were small and there was a marked depletion of depot fat. The kidneys were small, grey-tan to grey and the surfaces of some were granular. The livers were essentially normal, although in a few mice they appeared pale.

Microscopically, the kidneys revealed segmental dilatation of the cortical tubules, and between these regions there were areas of connective tissue scars in which there were strophic tubules and many glomeruli. Cloudy swelling was still present and some of the tubules contained granular casts. The glomeruli were

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relatively uninvolved. Other orgnas studied were essentially normal.

Tentatively, one may conclude that the daily ingestion of 80 mg of T as the nitrate by the mouse produces 1) an acute intoxication, in which some animals die, and 2) the remaining animals do not recover, but go over into a state of subacute intoxication, from which they may die. In the acute intoxication the kidneys (enlarged, pink-grey, smooth) are the seat of severe cloudy swelling or acute necrotizing nephrosis, while in the subacute stage, the kidneys (shrunken, grey, granular) are characterized by areas of cortical scars alternating with areas of dilated tubules with cloudy swelling and granular casts.

It is unfortunate that the mouse does not readily lend itself to a study of blood changes, so that one might attempt to ascertain whether the deaths are due to uremia or some other cause.

In general the clinical course of the animals, and the gross and microscopic pathological findings suggest that the continued ingestion of large dosages of T nitrate leads to a subacute intoxication . The dosages required to produce these latter changes appear to be well in excess of the dosages required to produce the acute intoxication. Whether or not the subacute changes described can be produced by subtoxic dosages ingested for a very long period is a question for future study.

Also to be considered is the fact that 80 mg of T as nitrate is a large daily dose for a mouse (possibly equivalent, depending on criteria of transposition, to approximately 1/10 to 1 pound of nitrate per day for a 70 kilo man). It seems entirely unreasonable to believe that a man would be permitted to be exposed under conditions that would allow even a fraction of this amount to enter his body daily. Indeed, from both our experiments and the lack of reports of acute toxicity in industry, it appears the the main practical problem is that of chronic, and not acute, toxicity.

A note on tests for detention of toxicity. Although our laboratory is not directly concerned with methods of detection of toxicity, the experimental results may offer some suggestions. We have previously stated the necessity of differentiating between the presence of T in the body and T toxicity. Although the amount of T present in the tissues and excreta is probably related to the degree of toxicity, the stage (and time factors) of toxicity must be considered. It is probable that a particular test of kidney function or dysfunction may be of great value in the acute intoxication (during the subacute or chronic stages, when the tubular epithelium may be more or less normal; a test based on a different function of the kidney or on dysfunction of other tissue might afford a better criterion for intoxication during these latter stages. Thus, it may be of importance to consider the length of time an individual has been exposed to T compounds, as well as his clinical condition, in deciding the type of test to be used in determining whether or not he has been poisoned by T.

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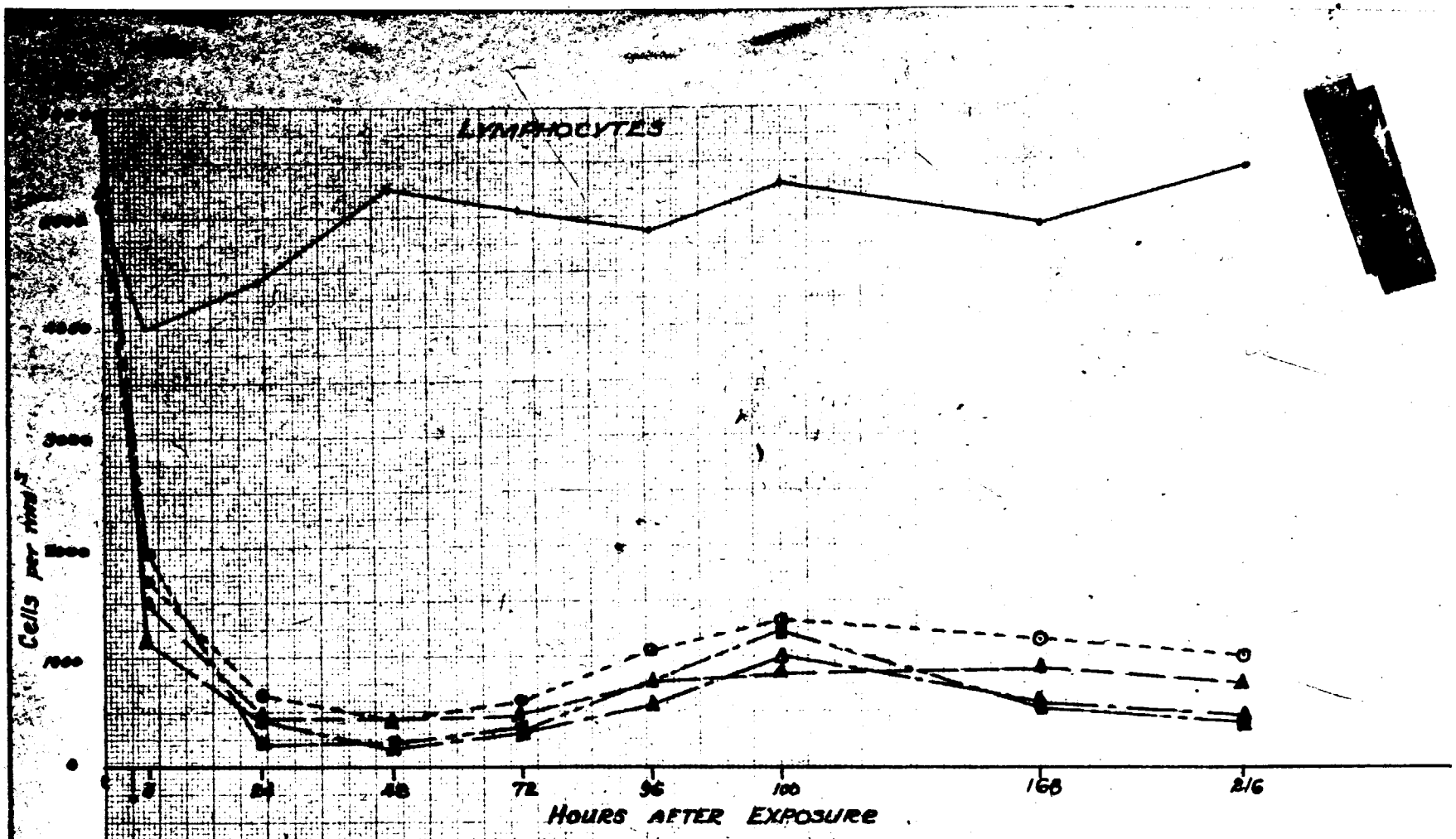

Dose	Number of Rabbits																							
Control	18	18			17				16				9				11				13				16				18
70-79n	18	17			17				14				10				10				9				13				14
85-95n	17	15			18				11				9				8				10				12				13
100-108n	6	7			8				8				6				5				4				6				8
128-142n	3	7			4				6				3								6				4				2

Key
- Control
- 70-79n
- 85-95n
- 100-108n
- 128-142n

FIGURE 2: Rabbits; LYMPHOCYTES after SINGLE Doses of FAST NEUTRONS

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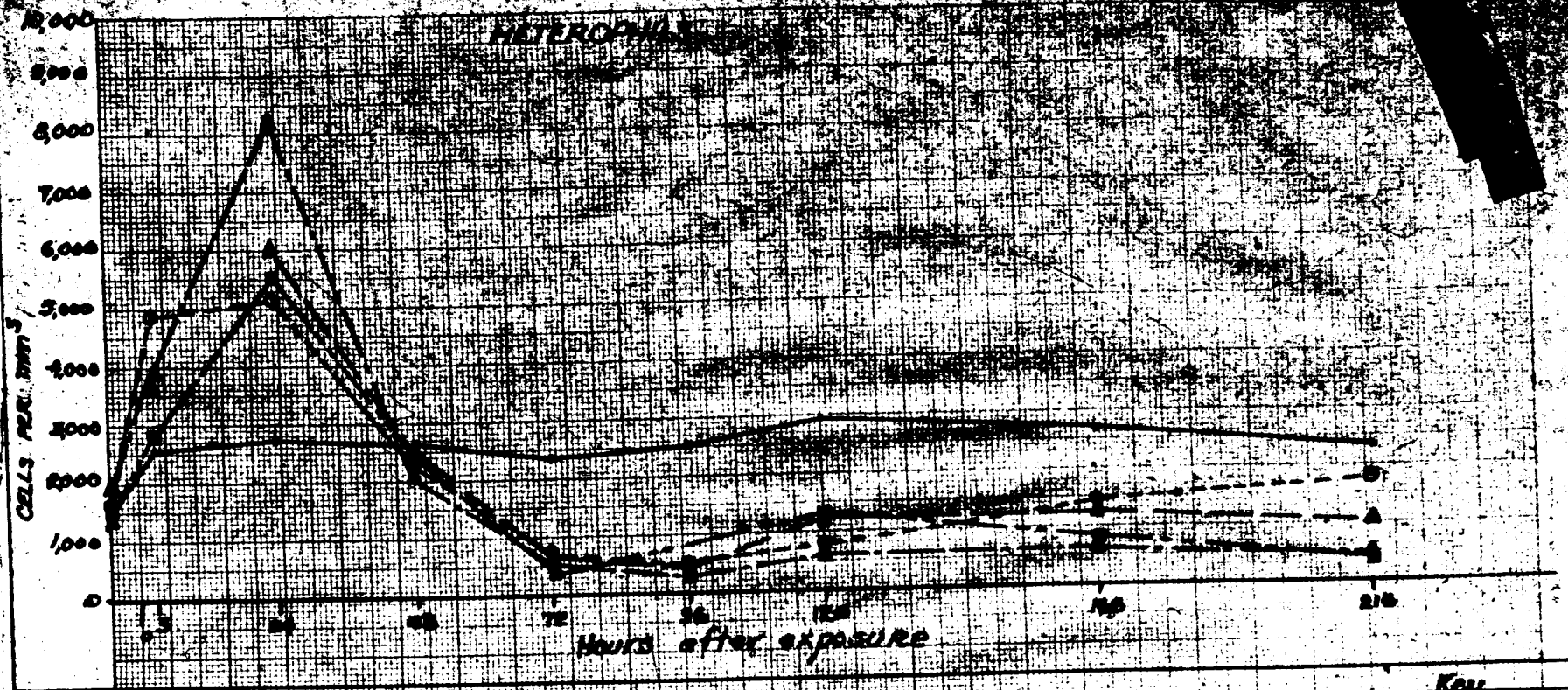
70n - 142n

CH-2447



Dose																								
Control	14	15		17		16		9		11		15		16		14								
70-79 h	14	17		17		14		10		10		9		15		13								
83-95 h	11	15		15		11		9		8		11		11		8								
100-108 h	8	7		8		8		6		5		9		6		6								
125-142 h	3	7		4		6		3				6		4		2								

Key
Control
70-79 h
83-95 h
100-108 h
125-142 h

FIGURE 1: RABBITS: HETEROPHILS AFTER SINGLE DOSES OF FAST NEUTRONS
70h - 142h

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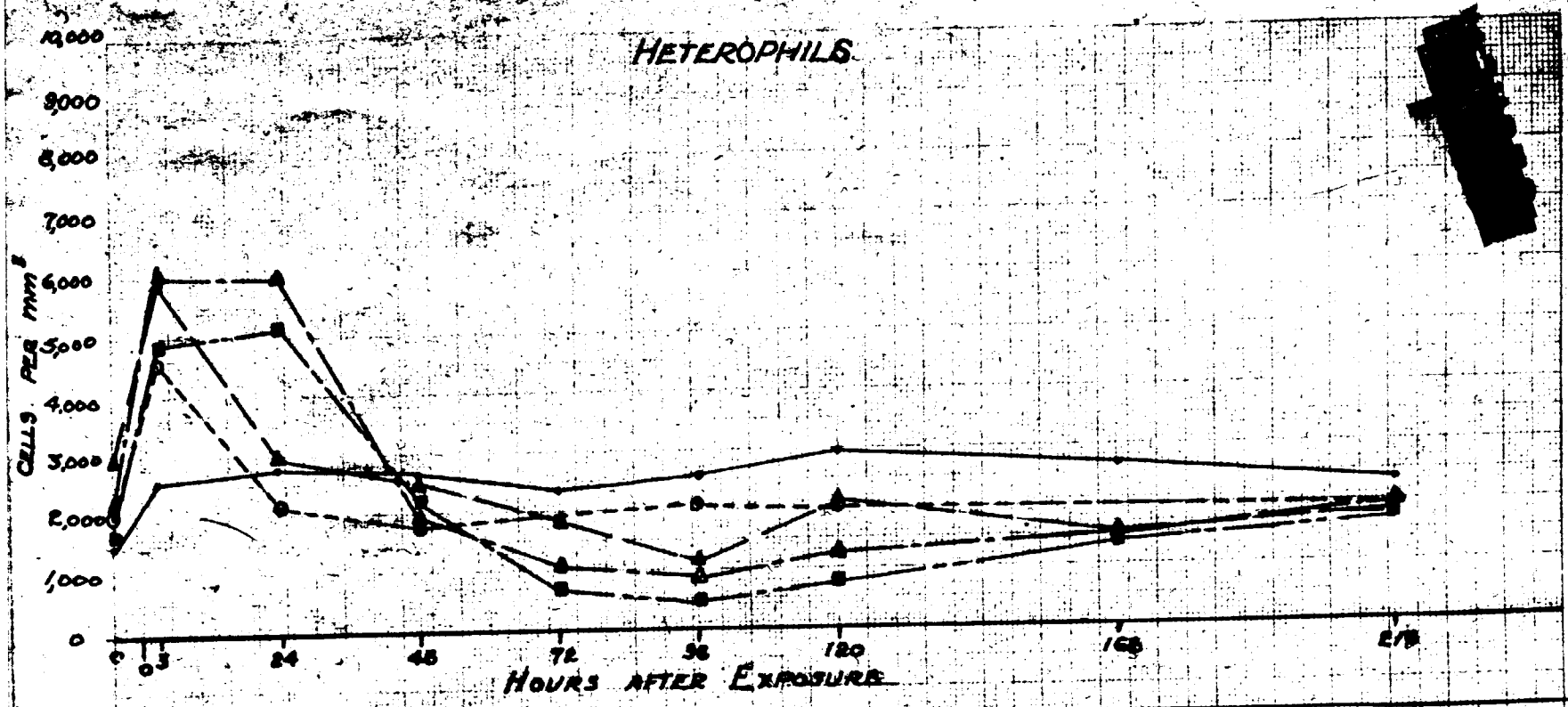

Dose	Number of Animals									
Control	14	15	17	16	9	11	13	16	18	
8-10 n	4	4	4	4		4	4		4	
26-28 n	6	6	6	6	4	2	3	6	5	
52-66 n	9	11	11	11	2	11	3	10	10	
70-79 n	15	17	17	14	16	10	9	13	14	

Key
- Control
- 8-10 n
- 26-28 n
- 52-66 n
- 70-79 n

FIGURE 4: RABBITS: HETEROPHILS AFTER SINGLE DOSES OF FAST NEUTRONS 8n - 79n

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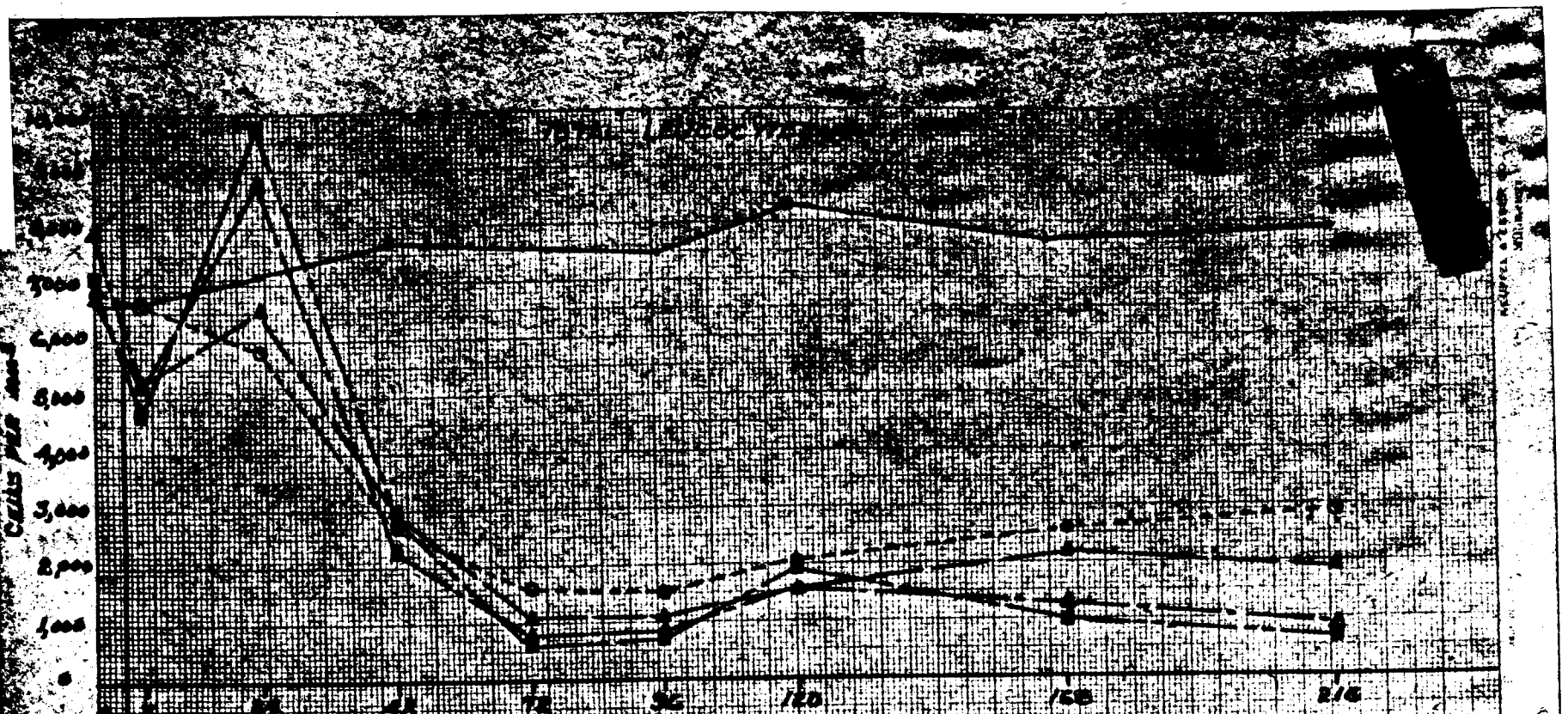

Dose	Number of Rabbits																							
Control	18	18	17	16	9	11	18	17	18	Key: Control
70-79 h	15	14	11	14	11	10	9	13	15	70-79 h
85-95 h	11	10	11	11	9	8	10	12	13	85-95 h
100-109 h	8	8	8	8	6	6	4	6	8	100-109 h
128-142 h	5	7	4	7	6	1	6	6	4	128-142 h

FIGURE 9: RABBITS: TOTAL LEUKOCYTES AFTER SINGLE DOSES OF FAST NEUTRONS

70 h - 142 h

OTB-8447