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and
Minnesota Medical Foundation


# Biochemical Effects of Radiations

Volume XX | Friday, June 3, 1949 | Number 30

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
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I.

# UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
## CALENDAR OF EVENTS

June 5 - June 11, 1949

No. 251

Sunday, June 5

9:00 - 10:00 Surgery Grand Rounds; Station 22, U. H.

10:30 - 11:00 Experimental Considerations of Restoring Continuity of Superior Mesenteric Vessels; Loren E. Nelson.

Monday, June 6

8:00 Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:20 Pathology Seminar; Paralytic Mychemoglobinuria; Donald Gleason; 104 I. A.

12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Class Room, Minneapolis General Hospital.

1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-109, U. H.

4:00 - Pediatric Seminar; Giant Cell Pneumonia; Robbie Green; 6th Fl., W., Child Psychiatry, U. H.

Tuesday, June 7

8:30 - 10:20 Surgery Reading Conference; Small Conference Room, Bldg. I, Veterans Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans Hospital.

12:30 - Pediatric-Surgery Rounds; Sta. I, Minneapolis General Hospital; Drs. Bosma, Wyatt, Chisholm, McNelson, and Dennis.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

1:00 - 2:30 X-ray Surgery Conference; Auditorium, Ancker Hospital.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:00 - 5:30 Physiology-Surgery Conference; Effect of Vagotomy on Gallbladder Motility; F. Johnson; Eustis Amphitheater, U. H.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Drs. Rigler, Stauffer, and Staff; U. H.; Todd Amphitheater, U. H.

Wednesday, June 8

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 9:30 Clinico-Pathological Conference; Auditorium, Ancker Hospital.

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans, Room 1AW, Veterans Hospital.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans Hospital.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

12:00 - 12:50 Radio-Isotope Seminar; Current Literature; Seminar Group; Rm. 212, Hospital Court, Temp. Bldg.

3:00 - Special Lecture; Intestinal Macrocytic Anemia; L. J. Witts, Oxford University, England; Todd Amphitheater, U. H.

3:30 - 4:30 Journal Club; Surgery Office, Ancker Hospital.

4:00 - 5:00 Infectious Disease Rounds; Main Lecture Room, Minneapolis General Hospital.

Thursday, June 9

8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Craig Freeman and H. M. Stauffer; M-109, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, Minneapolis General Hosp.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Class Room, Minneapolis General Hospital.

4:00 - Special Lecture; Non-Operative Treatment of Perforated Ulcer; Herman Taylor, England; Todd Amphitheater.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Drs. Peterson and Miller, Miller Hospital; Todd Amphitheater, U. H.

Friday, June 10

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Veterans Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department. U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Early Diagnosis of Tumors of the Stomach from the Roentgen Standpoint; F. J. Ruzicka; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Large Classroom, Minneapolis General Hospital.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 3:00 Pathology-Surgery Conference; Auditorium Ancker Hospital.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

4:00 - 5:00 Electrocardiographic Conference; George N. Aagaard; 106 Temp. Bldg., Hospital Court, U. H.

Saturday, June 11

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 20, U. H.

8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor, West Wing, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-101, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amph., U. H.

9:00 - 11:30 Surgery-Roentgenology Conference; Todd Amphitheater, U. H.

9:00 - 12:00 Psychiatry Conference; VA Hospital Annex, Fort Snelling.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

# II. SOME BIOCHEMICAL EFFECTS OF IONIZING RADIATIONS

Samuel Schwartz

The studies to be described herein were made at the Plutonium Project Laboratory (now the Argonne National Laboratory), Chicago, from 1943-1946, as part of the research program of the Manhattan Project. They aimed at the detection of the earliest and most sensitive changes possible in experimental animals and human subjects administered known amounts of radiation, and at the evaluation of changes found in experimental subjects and in project personnel.

The known chemical and biochemical effects of radiation have been reviewed in recent years by a number of investigators[1-8] *. Several biochemical systems have been shown to be affected by therapeutic doses. These involve the metabolism of carbohydrates[9-11], nucleic acids and purines[12-18], proteins and protein derivatives[1,19-20], electrolytes[21-26], cholesterol[27-29], histamine-like substances[30-32], and other compounds. The relation of these effects to acid-base balance[33-34], excretion of specific proteinases in urine[35], and diminished intestinal absorption[36-38], have also been described.

Though these reported studies have permitted some insight into the nature of radiation effects, very few seemed sufficiently sensitive or specific to be useful in detecting early "damage" to project personnel. A series of excursions into various fields of metabolism were therefore undertaken in the hope that they might yield clues for further and more comprehensive investigation. The tests chosen were intended to cover as wide a range of functions as practicable. At the same time it was hoped to keep them sufficiently simple to permit their application on a fairly wide scale with the least possible inconvenience to personnel.

*No attempt has been made here to review the literature since 1946.

The results of these studies have been reported in a series of Manhattan Project reports[39-46]. The present discussion aims only at a summary of these reports and at a discussion of their possible significance. Reference is made to the original reports for details of technique, for the complete experimental data, and for further bibliography.

## Experimental

### Part I

### Studies of experimental animals

Mongrel dogs were used for most of these investigations. Urine analyses were generally done on 24-48 hour collections of urine; 2-4 day collections were usually combined for fecal studies. Total body x-ray was administered under supervision of members of the biology section with a 200 kvp machine operated at 15 milliamperes. It was delivered at the rate of about 6 r per minute. One-half mm. of copper and 1 mm. aluminum filters were used.

The dogs were fed a diet of commercial dog biscuits (Friskies), generally supplemented with meat 1 or 2 times weekly.

The same animals were also investigated for hematological and physiological changes by other groups on the project.

#### A. The effect of Irradiation on Coproporphyrin Excretion

##### 1. Introduction

Previous reports have discussed the occurrence of increased coproporphyrin excretion following the administration of lead and certain other metals[47], and in conditions associated with increased erythropoietic activity[48]. In agreement with other published studies, it was found that, in the case of lead, excretion of the type III coproporphyrin isomer was increased, whereas, in the latter condition, ex-

cretion of the type I isomer was increased. On the other hand, certain metals such as uranium and thorium given in very large doses were found to produce a diminution in urinary porphyrin excretion. Studies indicated that the uranium effect was probably due in large part at least to impaired kidney function. The mechanism of the thorium action was not apparent.

We are not familiar with any studies in the literature on the effect of irradiation on coproporphyrin excretion. It seemed of interest to study this problem, first because of the known effect of irradiation on erythropoietic activity, and second, because various types of toxic conditions have been found to be associated with abnormalities in porphyrin excretion.

2. Experimental

a. The Effect of a Single Dose of Total Body X-Ray.

(1) The Effect of a Lethal Dose.

Four dogs were given a single dose of 400 to 450 r total body X radiation. All died in 2-3 weeks. In each instance, the per diem excretion of coproporphyrin fell within a week to less than 50 per cent of the average control value. Before death, values rose considerably in 2 of the dogs, but remained low in the other two. The data are summarized in Figure 1. To better illustrate the effect of irradiation, the data are plotted in all instances in terms of the per cent deviation of the per diem coproporphyrin excretion from the average control value for each dog. Each of the points plotted represents the average value of two consecutive determinations.

Studies were also made of 4 dogs given 300 to 350 r total body X-ray Three of the 4 dogs showed a considerable decrease in urinary coproporphyrin excretion following irradiation. The coproporphyrin excretion in the fourth dog showed extreme waves of variation in both control and post-irradiation periods.

To get a more complete picture of total porphyrin excretion, studies have been made of 3 bile-renal fistula dogs prepared for us by J. G. Allen. Irradiation was followed in all 3 instances by depression of the coproporphyrin excretion similar to that illustrated in figure 1.

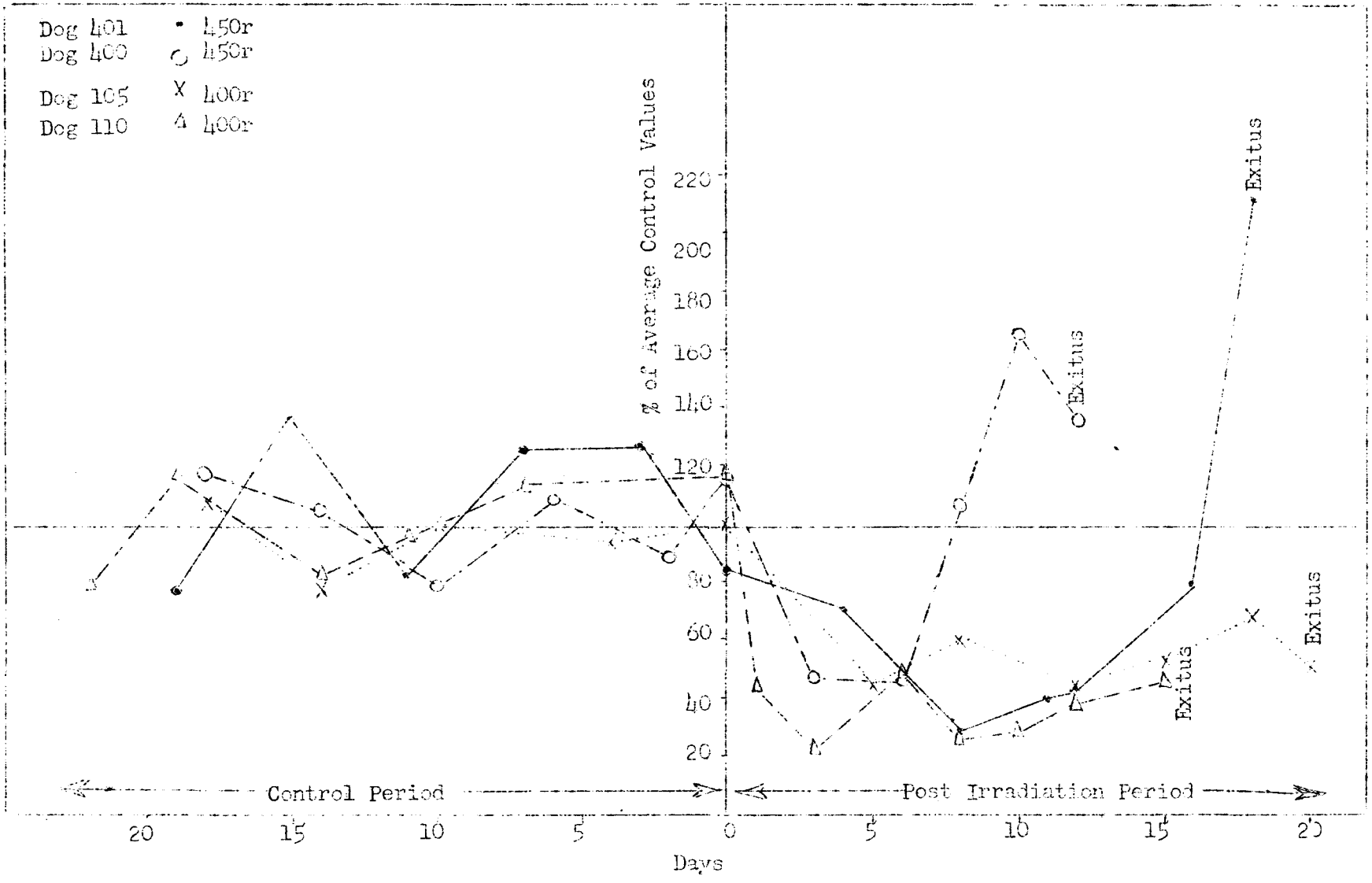
(2) The Effect of a Sublethal Dose. Two dogs were given 100 r total body X ray. Seven control determinations on dog 102 ranged from 15 to 35 micrograms per day, with an average value of 23 micrograms per day. The seven determinations following irradiation ranged from 11 to 20 micrograms per day, with an average of 15 micrograms per day. Dog 106 showed no significant change following receipt of 100 r. Two dogs given a single dose of 50 r showed no significant change in urinary coproporphyrin excretion.

b. The Effect of Daily Administration of Total Body X-ray.

(1) 50 r Daily. Three dogs were administered 50 r total body X-ray daily. All showed considerable reduction in urinary porphyrin excretion with a return toward normal before death. The data are illustrated in Figure 2.

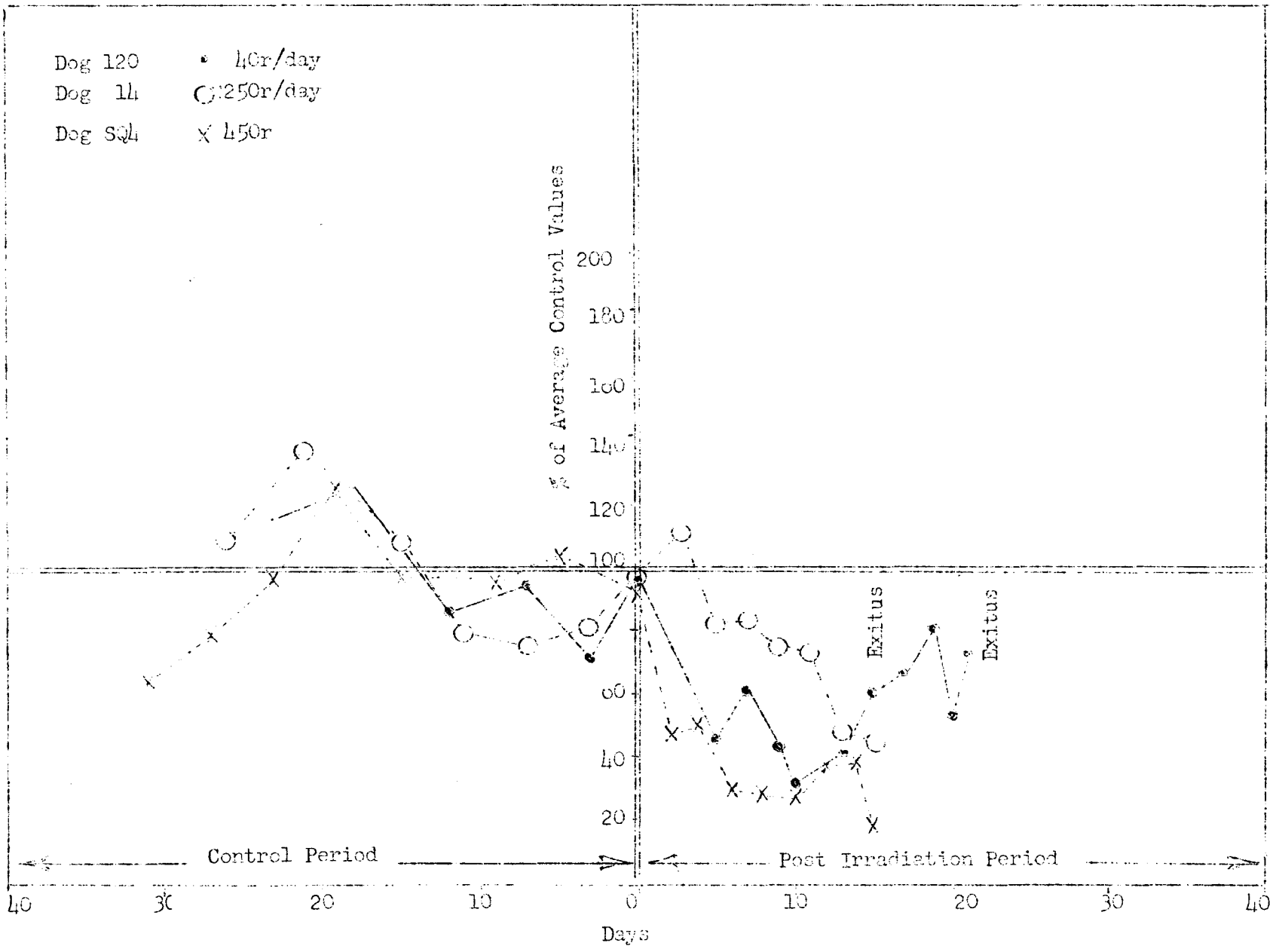
(2) 40 r Daily. Two dogs given 40 r total body X-ray daily showed a marked fall in porphyrin excretion after about 10 days. Values rose sharply before death.

(3) 25 r Daily. Two dogs which received 25 r total body X-ray daily showed no significant change in urinary porphyrin excretion.




The Effect of a Lethal Dose (400-450) of Total Body X-ray on Urinary Coproporphyrin Excretion
r

**Fig. 1**




The Effect of Total Body Irradiation on Coproporphyrin Excretion in Bile-Renal Fistula Dogs.

**Fig. 2**

(4) 12.5 r Daily. Two dogs were studied while receiving 12.5 r total body X-ray daily. One showed only a marked rise in urinary coproporphyrin excretion before death. In the other dog, porphyrin excretion rose for several months and then fell during the several weeks before death.

c. The Effect of a Lethal Dose of Strontium$^{89}$.

Two dogs given acutely lethal doses of $Sr^{89}$ have been studied. Dog 37 received 3.13 mc/kg, and dog 49 received 2.87 mc/kg. Excretion of coproporphyrin fell in both animals after administration of the $Sr^{89}$. The typical increase before death occurred in dog 37, while dog 49 showed only a tendency to return to the control average.

d. The Effect of a Lethal Dose of Plutonium.

Dogs number 42 and 48 received 0.418 and 0.766 micrograms of plutonium I.V. per kg body weight, respectively. A similar pattern of decreased coproporphyrin excretion was found in both prior to their deaths within 15 days.

e. The Effect of Irradiation on the Excretion of Fecal Porphyrins in Dogs.

The effect of irradiation on the fecal excretion of coproporphyria, protoporphyrin, and deuteroporphyrin has been studied in only a few of the above animals.

The excretion pattern of these porphyrins tended to be similar to, though not necessarily entirely parallel with, that of the urinary coproporphyrin; a period of diminished excretion was followed in some instances by a terminal rise.

It should be pointed out that the dogs commonly became constipated following irradiation. Decreases in per diem excretion values, therefore, may be associated with increases in actual concentration per 100 grams.

3. Discussion

The interpretation of the experimental data is not at all clear. It may be that the fall in coproporphyrin excretion is related to the inhibition of erythropietic activity. Thus, we have recently found a good correlation between reticulocyte count and red cell coproporphyrin concentration[49] and the increased excretion of coproporphyrin in relation to increased erythropoiesis is well documented. The course of the terminal rise in porphyrin excretion is unknown, but may be related to liver dysfunction, as will be noted subsequently.

At any rate, it is obvious that the fall in coproporphyrin excretion is not a sensitive index of radiation exposure. Actually, small exposures may result in elevated values. It seems, however, that the rapid terminal rise may be a bad prognostic sign.

It is likely that determination of the individual coproporphyrin isomers would yield further valuable data.

B. Studies of the Hemolytic Effect of Radiation

1. Introduction

Despite considerable study of the hematological effects of radiation there is still little fundamental information available on the nature of radiation anemia, especially as regards the relative importance of hemolytic and regenerative factors. This has been due chiefly to the fact that the investigative tools used heretofore have been limited largely to routine studies of the peripheral blood. This has tended to yield a relatively static picture that is merely the end result of a number of factors such as the rate of production, release from the bone marrow, and life

span of the red blood cells. Studies correlating bone marrow and peripheral blood findings are few, and biochemical investigations of red cell destruction have, to our knowledge, not been described. Even reticulocyte measurements have been reported in only rare instances.

Most investigators have stated that the anemias appearing both in humans and in experimental animals following administration of either external or internal radiation are due to suppression of the erythropoietic system, or to abnormalities of regeneration. However, while it is obvious that suppression of erythropoiesis occurs following administration of certain types and doses of radiation and may result in extreme aplasia of the erythroid elements in the bone marrow, it appears equally obvious that radiation anemia cannot be due to inhibition of erythropoiesis alone; a hemolytic component* must play a variable and often significant role in the development of both acute and chronic radiation anemia. Evidence for this assumption is threefold, vis., histological, mathematical and biochemical, as will appear in the following.

a. Histological Studies

(1) Bone Marrow Histology in Chronic Radium Poisoning.

Martland has described histological changes in the bone marrow of six individuals in the dial painting industry who died of chronic radium poisoning[50-52]. In the first case he found that, "There was entire replacement of the fatty marrow of the femur by actively regenerating tissue, a marrow hyperplasia of the megaloblastic type.**

He also observed that, "The spleen showed....diffuse fibrosis and slight increase in hemosiderin pigment." Before death peripheral blood study in this patient showed a hemoglobin value of 20 per cent and red blood count of 1,064,000.

In the second case Martland reported that, "Necropsy showed an intense replacement of normal adult fatty marrow by a red regenerating bone marrow. Histologically, the marrow was characterized by an enormous number of nucleated red cells, normoblasts and megaloblasts which showed a regeneration of the megaloblastic type." A hemoglobin value of 20 per cent and a red blood cell count of 964,000 were previously reported before the death of the patient[2]. Similar findings were also noted in his other cases.

Martland's evidence, therefore, consistently indicated heightened erythropoietic activity of the bone marrow in fatal radium poisoning in humans. Despite this evidence, however, he concluded after his first case that, "There is a stage of stimulation followed later by sudden exhaustion of the erythroblastic centers with production of a rapid fatal anemia." Of his second case (before the patient's death) he said, "It is due to exhaustion of the blood forming centers...." and even after necropsy examination showed the ".... intense replacement.....by a red regenerating bone marrow". He said of the irradiation that it, "...may go on for years before the centers are finally exhausted". This hypothetical "exhaustion" of the blood forming centers was also mentioned in the discussion of his later cases.

Martland was aware of this contradiction and pointed out in his 1929 review of the subject that, "The occurrence of this apparently hyperplastic marrow was puzzling since, heretofore in the report of anemias due to undue exposure to x-ray and gamma radiation from radioactive substances they have usually been described as distinctly aplastic in type. As in practically none

* In the present report the term "hemolysis" is used to indicate all types of red cell destruction, regardless of their nature.

** It is not clear whether these cells were true megaloblasts, or merely large cells.

of these cases was necropsy performed or study of the bone marrow made, this conception is purely a clinical one and may not always be substantiated by the facts as we know them."

Similar histological findings have been reported in experimental animals [53-54].

(2) Erythrophagocytosis Following Acute Radiation Exposure.

Heinicke in 1905[55] pointed out the occurrence of red cell destruction in rabbit bone marrow about 48 hours after acute x-ray exposure. Increased pigmentation in the spleen was also described. Other investigators have described similar phenomena. This problem has also been reviewed, along with the general problem of the hematological effects of radiation, by Selling and Osgood[55].

b. The Speed of Development of Acute Radiation Anemia.

While there is no unanimity regarding the life span of the red blood cells, most investigations have indicated that red cells remain in circulation for an average of 100, plus or minus 30 days. Assuming this figure to be correct, it is obvious that complete cessation of erythropoiesis alone would result in about one per cent fall in red blood count (or hemoglobin) per day. Reports from various laboratories indicate that during the period of most rapid development of anemia the rate of red count (or hemoglobin) fall may be much greater than this.

c. Biochemical Evidence of Increased Red Cell Destruction.

We are not familiar with any quantitative studies of bile pigment excretion in irradiated subjects that might be used as a measure of the rate of red cell destruction.

In a study of the effect of irradiation on cats, Wright and Bulman[57] noted that "....with fatal doses, a marked anemia usually develops several days before death. That this may be due to hemolysis is suggested by the greenish tinge of the plasma which frequently gives a positive Fouchet reaction and a positive indirect van den Berth for bilirubin."

Harold and Meiszner[58] quantitated total urine pigment according to Heilmeyer's method and, like Heilmeyer[59], found increased pigment excretion following local irradiation of five female subjects with uterine tumors. This was interpreted as being due to a hemolytic reaction. The quantitative interpretation of this data, however, is uncertain.

2. Experimental

The Effect of Total Body X-ray on Hemoglobin Metabolism in Dogs

a. Control Dogs

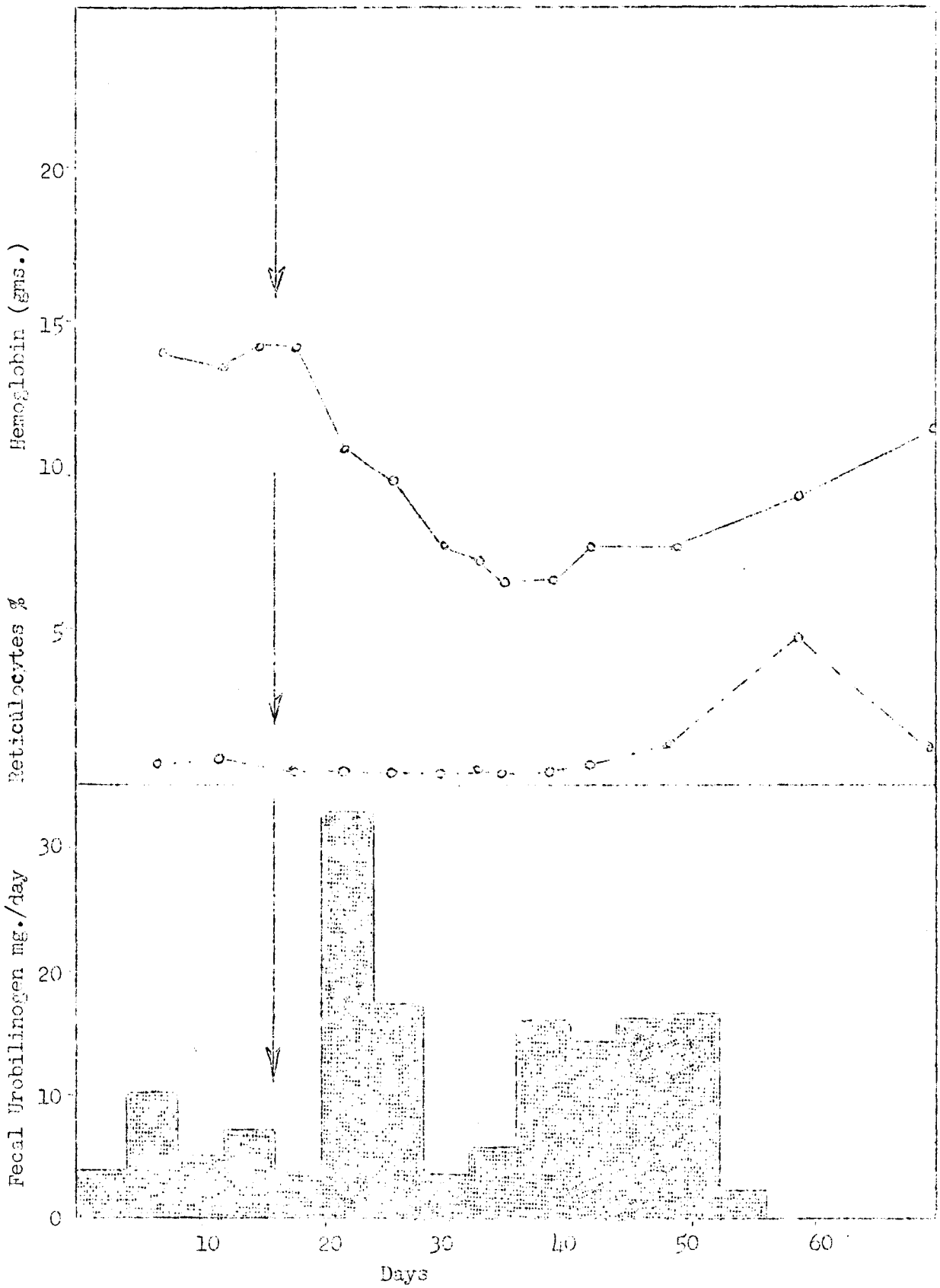
A total of 85 determinations have been done of fecal urobilinogen excretion in 18 control dogs. Most values ranged from 5 to 10 mg. per day with extremes of 1 to 25 mg. per day.

b. Irradiated Dogs.

In most dogs given a single large dose of total body X-ray an increased excretion of urobilinogen was found, especially from about the fourth to twelfth day. This is often, though not always, associated with a drop in the reticulocyte count. Data on one such dog are illustrated in Figure 3.

From the sixth to the tenth day after irradiation, the hemoglobin of dog 43 fell at an average rate of about six per cent per day. This compares with the data on several other dogs whose hemoglobin dropped for several days at a maximum rate of two to five per cent per day.

The interpretation of data on excretion of bile pigment is often difficult because many of the dogs become severely




The Effect on Hemoglobin Metabolism of 300r Total Body X-ray, Single Dose (Dog 43 )

Fig. 3

constipated. This is illustrated by dog #44 who was given 300 r total body X-ray. Four determinations during the sixteen day control period averaged 12 mg. per day. During the sixteen days after irradiation the average value was 26 mg. per day. In the last two day period the concentration rose to 170 mg. per cent, but because of marked constipation the per diem value for this period was only 22 mg. per day.

Terminal increases in fecal urobilinogen excretion may be associated with internal hemorrhage. This was most strikingly illustrated in dog 26 which died 72 days after daily treatment with 12.5 r total body X-ray was started. Subcutaneous hemorrhages were first noted 14 days before death, and considerable internal bleeding was found at the post-mortem examination. During the last 14 days of life the hemoglobin concentration fell precipitously from 11.2 to 4 grams per 100 cc. The fecal urobilinogen excretion during the lasy eight days averaged 120 mg. per day, the highest value yet found in dogs. It is, of course, impossible to say what proportion of this was due to the bleeding as against red cell destruction by the usual mechanisms.

Excretion of urinary bile pigment, likewise, was found to be affected by large doses of radiation. E. Painter, of the Biology Section, first called our attention to the excretion of a green urine in a dog to which plutonium had previously been administered. Green urine has been found quite consistently in dogs receiving large doses of radiation. Its appearance has been well correlated with a diminution in food intake. This may be explained by the finding of Kanasaki[60] and others that a decrease in liver glycogen results in the excretion of a green biliverdin-containing bile. Beckman spectro-photometric studies of the dog urine by M. Hagedorn indicated that this urine pigment was spectroscopically similar to, if not identical with, biliverdin. Further evidence for abnormal bile pigment excretion in the urine came in the course of studies in excretion of urinary coproporphyrin by these dogs. The ether extract of acidified urine from dogs receiving either external or internal radiation was commonly found to be green. Such a finding is rare in control dogs.

These investigations were supplemented by studies of bile pigment excretion in three bile-renal fistula dogs given a single dose of total body X-ray.

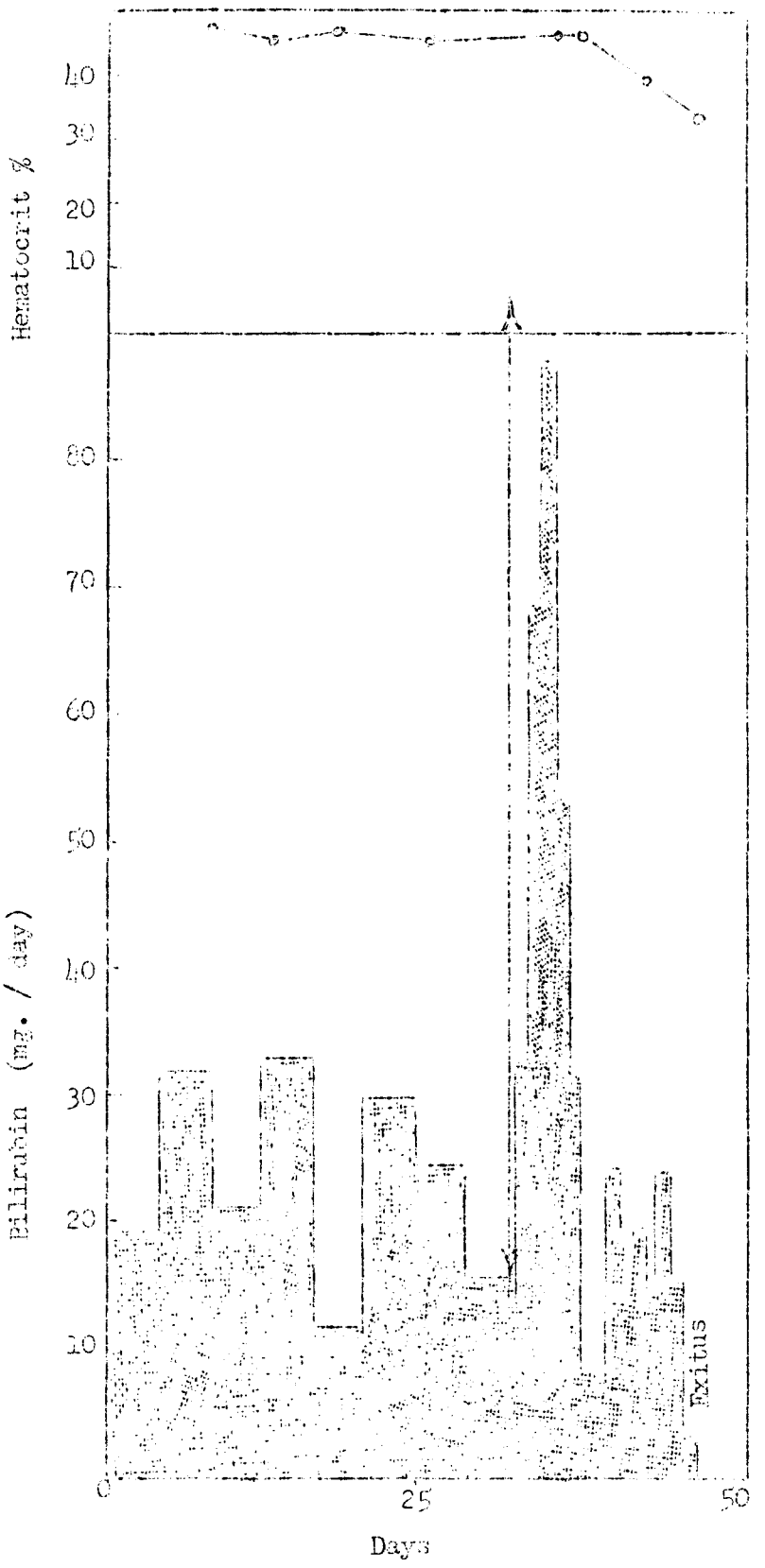
All three dogs showed significant increases in bile pigment excretion soon after total body irradiation, indicating the presence of some degree of hemolytic reaction. The data on dog SQ-5 is illustrated in Fig. 4. The operation performed on this animal was most successful as indicated by post-mortem examination.

Bilirubin excretion by the other two dogs rose to over 50 mg. per day in the few days after administration of 250 r total body X-ray. These values were at least twice as high as the highest control values in these animals.

### 3. Discussion

From the available data it is impossible to determine the relative magnitude of destruction of mature circulating cells as compared to that of immature cells within the bone marrow. In pernicious anemia, for example, it has been suggested that the increased fecal urobilinogen excretion may be due to excessive intramarrow destruction of young red blood cells. It may be, too, that such is the case in patients with anemia due to chronic radium poisoning.

In the studies reported here, there is no doubt that erythrocyte regeneration was interfered with. Otherwise, the great regenerative powers of the bone marrow would have been sufficient to maintain more nearly normal hemoglobin and red count levels, even with an increased rate of red cell destruction. It should be pointed out, however, that under some conditions the bone marrow responds even after administration of relatively large doses of radiation.




The Effect of 450r (Single Dose) Total Body Radiation on Hemoglobin Metabolism in a Bile-Renal Fistula Dog

**Fig. 4**

Dog 55 is illustrative in this regard. Following the development of an acute hemolytic anemia, due possibly to serum administration, the reticulocyte value rose and the anemia improved despite the continued administration of 25 r total body X-ray daily. Patients receiving $P^{32}$, likewise, were able to respond with an elevated reticulocyte count. Such a reticulocyte response, however, was not forthcoming in those dogs which received an acutely lethal dose of radiation.

Finally, it should be emphaaized again that the present discussion does not aim to minimize the importance of the erythropoietic inhibition caused by irradiation. It is intended, however, to indicate the necessity for considering still other mechanisms to account for both acute and chronic radiation anemia.

## C. Radiation-Induced Changes in Ultraviolet Absorption Spectra of Urine

### 1. Introduction

In a search for new clues regarding radiation effects, it seemed that studies of ultraviolet absorption spectra of urine might be especially promising, since changes in excretion of a large number of compounds might be simultaneously observed. Suggestive changes could then be further analyzed by appropriate chemical methods, or by further spectrophotometric studies following suitable purification.

### 2. Experimental

Aliquots of combined 24-hour urine samples were analyzed either following direct dilution or after suitable extraction. In most instances a 200 to 500-fold dilution with 6 N HCl was employed. In all instances a corresponding blank was prepared. Most careful consideration was given the region from 220 to 360 mu.

For purposes of analysis the spectra obtained were plotted on a semi-logarithmic scale since such a plot enables one to superimpose different curves without regard to their absolute extinction values, and thus to detect the qualitative changes in which we were primarily interested. Quantitative changes, of course, are also apparent from such a plot.

The typical ultraviolet absorption spectrum of acidified urine from non-irradiated dogs presents the rather monotonous picture of a general slope downward from 220 to 360 mu. There is generally a variable amount of flattening in the region of 245 and 270 mu and to a much lesser extent, at about 310 mu. In only rare instances, however, are actual peaks observed in these regions.

In dogs given lethal doses of either external or internal radiation, an increase in absorption in one or all of these regions is always found at some time before death unless death occurs too soon. These changes are shown in Figure 5 in which we have plotted the acid absorption spectra of the urine obtained before and at intervals after treatment of a dog (105) which died 20 days after receiving 400 r total body X-ray. Spectrum (a) is typical of the 8 control spectra studied. Spectrum (b), obtained 6 days after treatment, is essentially within the control range. In spectrum (c) a relative increase can be seen in the absorption in the region of 245 mu. This became progressively more pronounced as death approached and in (d) an actual maximum is noted at 245 mu. In this latter spectrum a slight relative increase in the absorption in the regions of 280 mu and 310 mu is also apparent.

Some of the most interesting spectra were observed in dogs which were irradiated daily or which were injected with radioactive compounds. In Figure 6 are shown three such spectra. Dog 31 (a) received $12\frac{1}{2}$ r of total body X-ray daily for 209 days. He was moribund at the time this sample was obtained. Dog 38 (b) died 234 days after receiving 0.36 mc plutonium intramuscularly. This urine

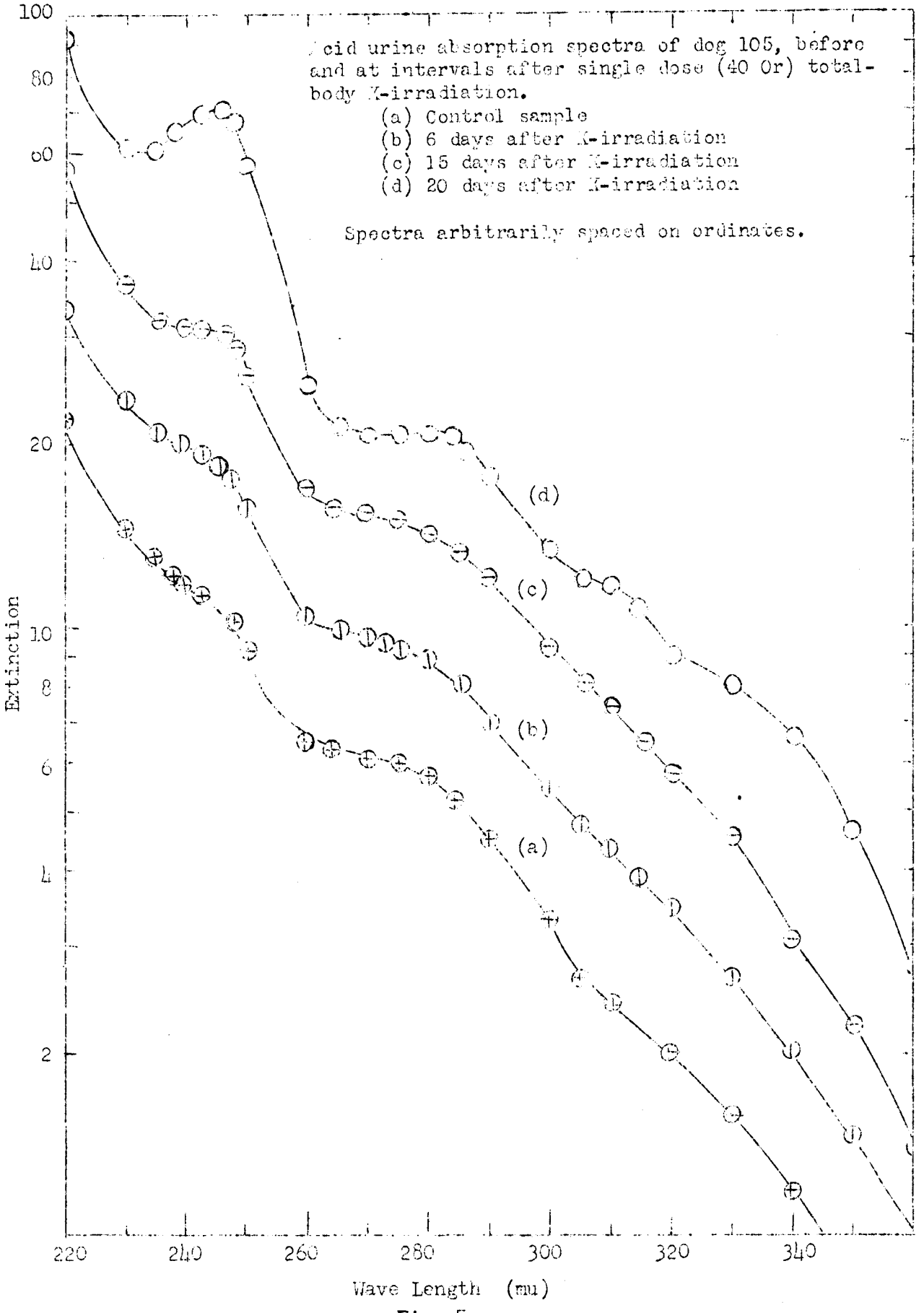

Acid urine absorption spectra of dog 105, before and at intervals after single dose (40 Or) total-body X-irradiation.
(a) Control sample
(b) 6 days after X-irradiation
(c) 15 days after X-irradiation
(d) 20 days after X-irradiation
Spectra arbitrarily spaced on ordinates.
Extinction
100
80
60
40
20
10
8
6
4
2
(a)
(b)
(c)
(d)
220
240
260
280
300
320
340
Wave Length (mu)

Fig. 5

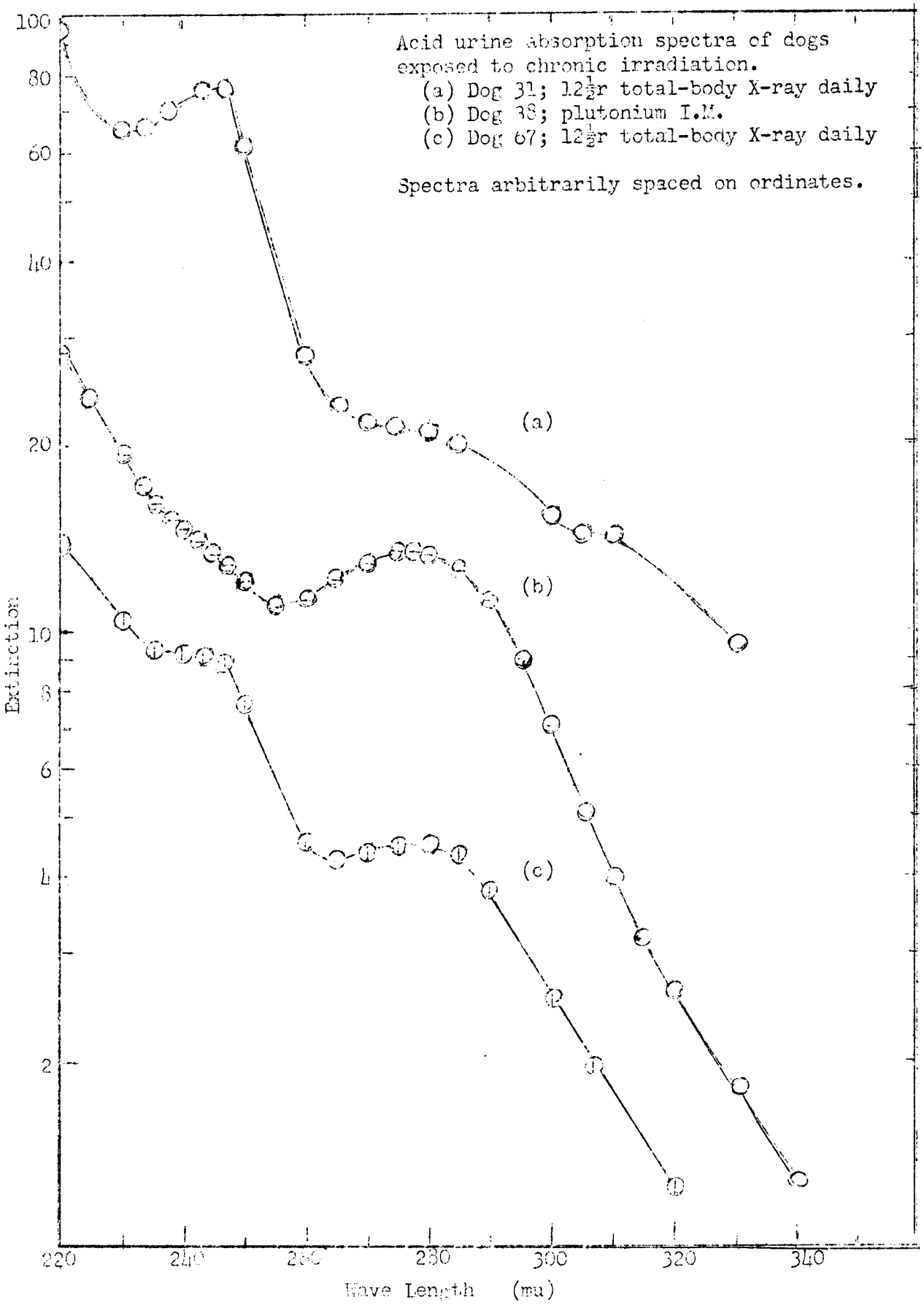

Acid urine absorption spectra of dogs exposed to chronic irradiation.
(a) Dog 31; 12½r total-body X-ray daily
(b) Dog 38; plutonium I.M.
(c) Dog 67; 12½r total-body X-ray daily
Spectra arbitrarily spaced on ordinates.
(a)
(b)
(c)
Extinction
100
80
60
40
20
10
8
6
4
2
220
240
260
280
300
320
340
Wave Length (mu)

Fig. 6

sample was obtained on the day before death. Dog 67 (c) died on the 97th day of treatment with 12½ r total body X-ray daily. This sample was obtained two days before death. In the latter two instances the increased absorption at 280 mu is especially marked; in the former instance the increase at 245 mu is more prominent. The control and early post-irradiation samples in all three dogs had absorption spectra essentially similar to that shown in Figure 1-(a) (control).

The compound responsible for the specific absorption in the regions of 245 mu and 310 mu has been identified as kynurenic acid, a derivative of tryptophane, on the basis of its ultraviolet absorption spectrum, its solubility characteristics, and its crystal form and melting point. The compound responsible for the increased absorption at 280 mu has been identified as uric acid. Identification was based on its specific destruction by incubation with uricase.

A spectrophotometric method was developed for the quantitative determination of urinary kynurenic acid. As shown in Table 1, elevated values were characteristic of the terminal period.

Table 1

A Comparison of Control and Terminal Kynurenic Acid Excretion in Irradiated Dogs.

| Dog # | Control Period | | Terminal Sample | |
|---|---|---|---|---|
| | mg% (ave.) | mg/day (ave.) | mg% | mg/day |
| 105 | 18 | 55 | 120 | 187 |
| 110 | 11 | 30 | 32 | 53 |
| 123 | 47 | 59 | 160 | 189 |
| 111 | 15 | 24 | 40 | 42 |
| 30 | * | * | 28 | 13 |
| 47 | * | * | 49 | 39 |
| SQ-4 | 10 | 42 | 25 | 18 |
| 120 | * | * | 15 | -- |
| 67 | 13 | 13 | 108 | 184 |
| 26 | -- | -- | 91 | 170 |

*Amount too small to determine (less than 5 mg%)

Dogs 105 and 110: Single dose, 400 r total body X-ray
Dogs 123 and 111: Single dose, 350 r total body X-ray
Dogs 30 and 47: Daily doses, 50 r total body X-ray
Dog SQ-4: Single dose, 350 r total body X-ray (Bile-renal fistula)
Dog 120: 40 r daily (Bile-renal fistula)
Dogs 67 and 26: 12.5 r daily

## D. The Effect of Lethal Doses of Total Body X-ray on Uric Acid and Allantoin Excretion in Dogs

### 1. Introduction

Several investigators have described an increase in excretion of uric acid, which in man is the end-product of purine metabolism, following radiation therapy of patients with leukemia or neoplastic disease. We are not familiar with any pertinent studies in irradiated human subjects with no such large masses of nuclear-rich and radio sensitive tissues which might serve as an important source of uric acid.

Reis and Kluge[16] reported an increase in concentration of uric acid in rat

sarcoma after the animals were irradiated with X-ray. Little if any significant decrease in concentration of allantoin was observed. Lommel[61] described an early increase followed by a later fall in excretion of uric acid after the administration of a lethal dose of X-ray to growing dogs. Allantoin excretion was not measured.

We are familiar with only a single study of excretion of both uric acid and allantoin in irradiated experimental animals. Miyazaki, in 1937[17] reported a decrease in uricolytic index* in the early post-irradiation period in rabbits given sublethal doses of X-ray. Excretion of both uric acid and allantoin was increased.

## 2. Experimental

Excretion of uric acid and allantoin was measured in seven adult mongrel dogs and in three rabbits.

Uric Acid. Color developed by a method essentially similar to that of Folin's for uric acid, was measured before and after incubation of urine with uricase. The true uric acid value is given by the difference of these two measurements; the so-called "non-uric acid fraction" is a measure of the color produced after incubation with the uricase.

Allantoin. The method of Young and Conway was used for the quantitative estimation of urinary allantoin.

### (1) Uric acid and Allantoin Excretion by Dogs Given A Single Acutely Lethal Dose of Total Body X-ray.

Five dogs (Nos. 400,401,105,110 and 123) were given a single dose of 350 to 450 r total body X-ray. All died after 13 to 21 days. In every instance there was an increase in the per diem excretion of uric acid 3 to 6½ days before death. No consistently significant change was found in the excretion of allantoin. The uricolytic index consequently dropped terminally in all the animals.

Consecutive determinations were made of all urine samples from only two of the dogs; studies in the other three animals were incomplete but appear sufficient to indicate definite trends. A typical experiment is summarized in Table 2.

Table 2

Uric Acid and Allantoin Excretion and Uricolytic Index in a Dog (401) given a single dose of 450 r total body X-ray

| Date | Uric Acid | | Allantoin | | Uricolytic Index |
|---|---|---|---|---|---|
| | Mg% | mg/day | mg% | mg/day | |
| 3/29-4/1 | 9.1 | 25.3 | 167 | 480 | 95 |
| 4/2-5 | 11.9 | 25.0 | 251 | 530 | 96 |
| 4/6-9 | 10.1 | 18.5 | 178 | 315 | 95 |
| 4/9: 450r | | | | | |
| 4/10-12 | 18.2 | 25.3 | 209 | 280 | 93 |
| 4/13-15 | 17.7 | 21.0 | 254 | 297 | 94 |
| 4/16-18 | 7.6 | 30.3 | 100 | 393 | 93 |
| 4/19-20 | 12.0 | 22.5 | 163 | 300 | 94 |
| 4/23 | 15.5 | 36.0 | 143 | 340 | 91 |
| 4/24 | 12.8 | 67.0 | 51 | 270 | 81 |
| 4/25 | 76.2 | 114.0 | 327 | 490 | 82 |
| 4/27 | 21.3 | 28 | 125 | 160 | 86 |

*The uricolytic index is equal to 100 times the concentration of allantoin nitrogen divided by the sum of the concentrations of allantoin nitrogen and uric acid nitrogen.

(2). Uric Acid Excretion by Dogs Given Slowly Lethal Deoses of Either External or Internal Irradiation.

One dog (no. 31) given 12.5 r total body X-ray six days per week until his death at the end of nearly seven months, showed an increased uric acid excretion during the last six days of life. (To 103 mg/day.)

Studies were made of one dog (No.38) administered intramuscularly 0.404 mg plutonium per kg body weight. Samples passed $3\frac{1}{2}$ months after plutonium injection had an unusually high concentration of uric acid, which continued high until death, $4\frac{1}{2}$ months later. Until the last week of life, however, the per diem output remained within normal range because of consistently small urine volume. The value for the last day of life was 472 mg per day, the highest value found in any of our dogs.

The excretion of compounds which are not destroyed by uricase but which give a color reaction by Folin's method does not appear to be influenced in any consistent way by exposure of dogs to a lethal dose of X-irradiation.

(3.) Uric Acid Excretion in Irradiated Rabbits

Studies were made of uric acid excretion in rabbits given either a single or repeated dose of 600 r total body x-ray. The estimation of allantoin in the same animals gave such inconsistent values from day to day that these data have been discarded.

The excretion pattern was different from that seen in the dogs; a prompt fall in urinary uric acid excretion followed the irradiation and persisted for a fairly long time even when the food intake had risen to nearly the control value.

3. Discussion

The experimental results described in the preceding section point to four main conclusions. (1) There is an increase in the per diem excretion of uric acid as well as of the ratio of uric acid to allantoin during the terminal period in dogs given a lethal dose of radiation. (2) Under the conditions of our studies there was no significant change in the excretion of total uric acid and allantoin in the irradiated dogs. The uricolytic index, therefore, fell significantly in all. (3) Uric acid excretion was diminished in rabbits given 600 r. (4) There was no significant or consistent change in the excretion of uric acid or allantoin in dogs in the period immediately following irradiation.

Bollman and Mann have shown that the conversion of uric acid to allantoin in dogs is largely dependent on the liver. In the dogs studied the consistent decrease in the uricolytic index during the terminal period was accompanied in all cases by a terminal increase in the excretion of urinary urobilinogen. The fall in uricolytic index, like the rise in urinary urobilinogen, was therefore probably due to liver dysfunction.

Since we do not know the purine content of the commecial ration given our animals, it is impossible to draw up an exact purine balance sheet. Lennox has described uric acid retention in fasting human subjects. Morgulis and Edwards found an increase in blood uric acid of dogs during fasting. The data on food intake, therefore, indicate that had food consumption been maintained, total purine excretion might have shown a considerable rise.

Rabbits appear to be poorly suited for studies of purine metabolism. The non-uric acid color was relatively high, often amounting to over 50 per cent of the total color produced. In addition the large amount of urinary sediment proved troublesome. The reason for the

inconsistency in daily allantoin excretion is unknown.

Undoubtedly the value of studies such as herein described would be greatly enhanced if the food intake could be kept constant throughout the period of investigation. As is well known, however, anorexia develops, especially in the period immediately following irradiation, and again in the terminal period. One might resort completely to parenteral feedings, i.e., of "fortified" plasma, but even this might introduce undesirable complications.

A study in which biopsy specimens of the liver at various stages after irradiation are assayed for uricase activity would probably fix the role of the liver with more certainty.

E. The Effect of Radiation On Liver Function.

1. Introduction

Most investigators agree that the liver is one of the more radio-resistant tissues of the body. The histological basis for this opinion has been summarized by Warren[62]. In the report by the histology group of the Metallurgical Laboratory[63] Miss R. P. Rhoades states that "In view of the meager evidence to the contrary it is concluded that alterations in the liver after irradiation from external sources are a secondary reaction of that organ, and that the liver epithelium is highly resistant." In the same study it is pointed out that definite microscopic changes were found in the larger hepatic cells of Amphiuma. It is not clear whether this is an example of a species difference or whether visualization of abnormalities was easier in these large cells.

The other point of view has probably been best summarized by Ellinger, who lists 126 references in his review of the response of the liver to radiation[64]. As he points out, considerable evidence of liver damage has been derived from the use of special staining techniques including those for sudanophile fat and glycogen, and from supravital staining. Isolated reports of functional impairment, i.e., increased urobilinuria, have also been made.

It should be emphasized that hepatic injury is probably the outstanding feature of subacute and chronic plutonium poisoning in mice and rats[65]. Here jaundice and anasarca have commonly been found from a few months to 2 years after plutonium administration. Death of the animals 1 to 2 months after administration has been considered due chiefly to hepatic failure.

A similar picture has been reported in animals administered other alpha-emitting fission products which, like plutonium, tend to localize in the liver.

Evidence of liver dysfunction has recently been reported in individuals exposed to the radiations of the atomic bombs in Hiroshima and Nagasaki. Keller[66] states that "abnormal amounts of urobilinogen in the urine were found in 9 of 11 patients." Reversal of albumin globulin ratios and increased indirect van den Bergh reactions were also reported. Unfortunately, however, no quantitative data were given.

Timmes[67], in a preliminary report from Nagasaki, notes that "bile" was frequently found in the urine. Again, no quantitative data were given.

2. Experimental

(1) The effect of ionizing radiations on urobilinogen excretion:

In general, significant increases in urinary excretion of urobilinogen were found only during the terminal period in animals dying of radiation exposure. In a few instances elevated values were found also during the first few days following a single lethal dose.

(A) Plutonium Studies: Four dogs received a lethal dose of plutonium. Dog 38 received intramuscularly 0.404 mc

per kg body weight. The animal died 234 days after injection. At autopsy its liver appeared markedly shrunken. Using only the usual histological techniques, no other microscopic abnormalities were noted. Excretion of urinary urobilinogen was considerably elevated, especially in the late stages.

This dog also excreted the highest concentration of uric acid (to 472 mg per cent compared with usual control values of less than 30 mg per cent), and presumably had the lowest uricolytic index (allantoin N x 100/allantoin N + uric acid N) of any of the dogs studied[8].

Dog 39 received 0.287 mc plutonium per kg intravenously. It died 90 days later. The urinary urobilinogen excretion data for this dog are summarized in Figure 7.

Dogs 42 and 48 received intravenously 0.418 and 0.766 mc Pu per kg body weight, respecitvely. Only the former showed a marked rise in urobilinogen excretion during the following several days.

(B) Total Body X-ray

(I) Single lethal dose: Urinary urobilinogen excretion was studied in ten dogs given a single dose of 300-450r total-body x-radiation. All died within 13-76 days. The data are summarized in Table 3.

Table 3

Urinary Excretion of Urobilinogen in Dogs Given A Single Lethal Dose of Total-body X-ray

| Dog # | Dose (r) | Survival (Days) | # Analyses | Control Period | | | | Post-Irradiation Period |
|---|---|---|---|---|---|---|---|---|
| | | | | mg % | | mg per day | | |
| | | | | Range | Ave. | Range | Ave. | Comments |
| 400 | 450 | 13 | 8 | 0.01 - 0.13 | 0.04 | 0.01 - 0.25 | 0.07 | Values of 1.41 and 1.23 mg % last 2 days of life. |
| 401 | 450 | 17 | 8 | 0. - 0.11 | 0.03 | 0. - 0.21 | 0.07 | 0.16 and o.31 mg % (0.75 and 0.41 mg/day) last 2 days of life. |
| 105 | 400 | 22 | 7 | 0.02 - 0.09 | 0.04 | 0.03 - 0.19 | 0.12 | Concentration possibly elevated only last day (0.14 mg %). |
| 110 | 400 | 15 | 8 | 0. - 0.09 | 0.03 | 0. - 0.20 | 0.07 | Elevated concentration only last 2 days (0.49 mg% on combined sample). |
| 111 | 350 | 14 | 12 | 0.- 0.11 | 0.05 | 0. - 0.21 | 0.08 | 0.24 mg % (0.41 mg/day) last day. |
| 130 | 350 | 113 | 13 | 0.02 - 0.11 | 0.04 | 0.02 - 0.24 | 0.09 | Average 0.24 mg/day 2-6 days before death. |
| 60 | 350 | 22 | 5 | 0.04 - 0.10 | 0.06 | 0.13 - 0.44 | 0.24 | Increase to 0.72 mg % (1.72 mg/day) last 4 days (combined sample). |
| 65 | 350 | 32 | 3 | 0.01 - 0.17 | 0.08 | 0.02 - 0.63 | 0.30 | 0.72 mg % (2.8 mg/day) 8 to 12 days after treatment. No analysis last 2 days. |
| 44 | 300 | 17 | 7 | 0.03 - 0.18 | 0.10 | 0.07 - 0.40 | 0.23 | Elevated concentration last 5 days. Final 2 day value 1.27 mg %. |
| 43 | 300 | 76 | 7 | 0.02 - 0.22 | 0.09 | 0.04 - 0.71(?) | 0.35 | No significant increase. |

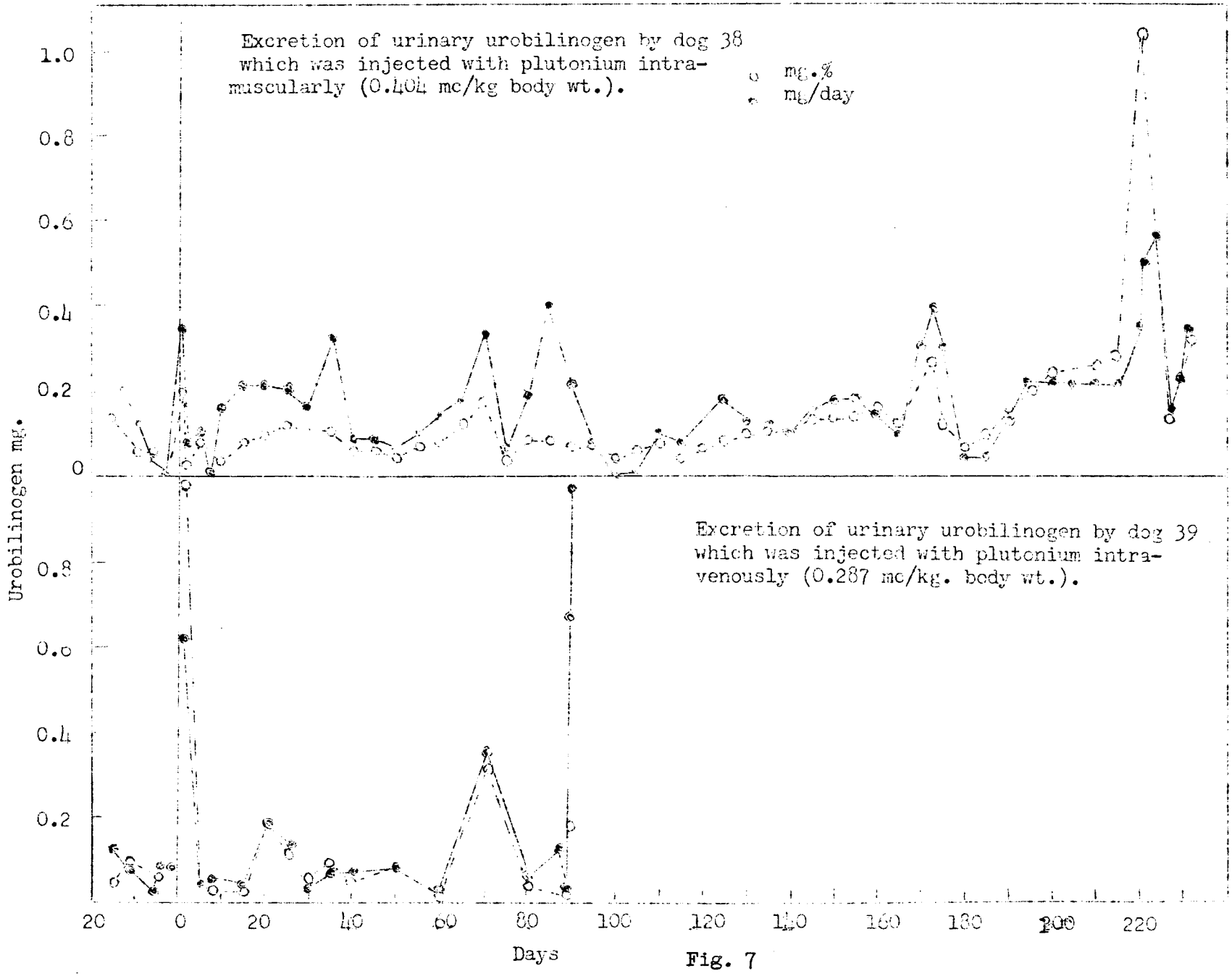

Excretion of urinary urobilinogen by dog 38 which was injected with plutonium intramuscularly (0.404 mc/kg body wt.).
mg.%
mg/day
Excretion of urinary urobilinogen by dog 39 which was injected with plutonium intravenously (0.287 mc/kg. body wt.).
Urobilinogen mg.
1.0
0.8
0.6
0.4
0.2
0
0.8
0.6
0.4
0.2
20
0
20
40
60
80
100
120
140
160
180
200
220
Days

Fig. 7

From this data it is seen that terminal increases in urobilinogen excretion were found in eight of the nine dogs on which urine studies were made to the last day before death. In the one negative instance (dog 43), elevated values after irradiation were matched by equally elevated values during the control period.

Urinary urobilinogen excretion was studied in two rabbits given lethal doses of total body X-ray. Animal 2802 had control values which were all under 0.07 mg.%. Values of 0.24, 0.26, and 0.22 mg % were found respectively during the last 3 days of life.

(2) Daily Administration, lethal dose.

Seven dogs were given 12.5 to 50 r daily until death. Four showed significant terminal increases in the excretion of urinary urobilinogen (0.27-0.84 mg %). Two had increases only 2-4 weeks after the start of treatment, and one showed no significant change at any time.

(3) Single sublethal dose.

In two dogs, sublethal doses of 209 and 250 r respectively were followed by moderated increases in excretion of urinary urobilinogen. No change was noted in a third dog given 100 r total body X-ray.

Serum tests of liver function in experimental animals.

Serum from control dogs, rabbits, and rats normally has a 2-4 plus cephalin flocculation reaction. A serial dilution technique employing either 4 or 8 tubes was therefore developed to get concentrations of serum which would yield 0-1 plus reactions. The data on control subjects in various species is summarized in Table 4. As noted in this table, normal human serum is unique in producing increased flocculation at certain dilutions. (Indeed, preliminary evidence indicates that additional information regarding liver dysfunction in humans may be obtained on this basis). The use of a higher concentration of dog serum results in decreased flocculation.

The effect of 1000 r total body X-ray given in 2 doses of 500 r each was studied in 47 rats. Another 13 received only a single dose of 500 r. 139 determinations of the cephalin flocculation reaction (4-tube technique) were performed over a period of 40 days. 115 analyses were done on 40 control rats during the same period. At times it seemed that changes were present in the irradiated series, but these were neither striking nor consistent.

No significant changes were noted in the thymol turbidity or colloidal gold reactions of sera from dogs receiving either external or internal irradiation.

## Part II

## Studies of Human Subjects

### A. Studies of Los Alamos Personnel with Accidental Radiation Exposure

In September, 1945, and again in May, 1946, accidents in the Los Alamos Laboratory resulted in severe overexposure of personnel to penetrating radiations. One death resulted in each instance. In the latter case clinical changes also occurred in 3 of the survivors. The clinical courses of these patients will be described elsewhere in the paper.

Chief interest in these studies related to the urinary excretion of oxysteroids. These studies were stimulated by a report by Talbot, et al[68] on the increased excretion of certain "corticosteroid-like" compounds in patients with hyperfunction of the adrenal cortex. Especially high values were found in patients with severe thermal burns.

Our studies of these compounds were limited almost entirely to the Los Alamos group. Because all but 1 of the urine

Table 4

Typical Sera Reaction in Humans, Dogs, Rabbits, and Rats Using a Modified Cepahlin flocculation Reaction

| Source | Tube Number | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) |
| Human 1. | 0 | 0 | 3 | 3 | 3 | 3 | 3 | 0 |
| 2. | 0 | 0 | 2 | 2 | 2 | 1 | 1 | 1 |
| 3. | 1 | 1 | 2 | 2 | 2 | 2 | 0 | 0 |
| Dog I-1. | 3 | 3 | 4 | 4 | 4 | 3 | 3 | 0 |
| I-2. | 4 | 3 | 3 | 3 | 3 | 2 | 1 | 0 |
| D-3. | 4 | 4 | 3 | 3 | 3 | 2 | 2 | 1 |
| Rabbit I-5. | 4 | 4 | 3 | 1 | 1 | 0 | 0 | 0 |
| R-3. | 4 | 2 | 1 | 0 | 0 | 0 | 0 | 0 |
| I-12. | 4 | 4 | 2 | 2 | 2 | 1 | 0 | 0 |
| Rat 9563. | 3 | | 1 | 0 | | | 0 | |
| 9558. | 3 | | 2 | 0 | | | 0 | |
| 9648. | 3 | | 1 | 1 | | | 0 | |

samples became available just as our group was disbanding in the spring of 1946, exhaustive studies were impossible. Instead, the urine was partially fractionated as described by Talbot et al and studied spectrophotometrically, using a Beckman spectrophotometer. Special emphasis was given the spectrum from 220 to 350 mu.

Case I.

Only a single urine sample, passed the day before death, was available from the first patient. It showed the following abnormalities.

a. Urinary "Steroid" Fraction.

The most interesting abnormality was in the ultraviolet absorption spectrum of the so-called "corticosteroid" fraction. As shown in Figure 8, there was a marked increase in specific absorption at about 230 mu. In addition, a bifurcated peak was present at about 320 and 330 mu. Shown in the same figure, for comparison purposes, are spectra from similarly prepared extracts of urine from Case II of the Los Alamos series, from a patient with severe thermal burns which proved lethal 5 days after the first urine sample was obtained (Case 13), and from 2 supposedly normal individuals (Cases 6 and 12). These data are described in more detail below.

b. Urinary Coproporphyrin. A value of 21 micrograms per cent coproporphyrin (252 micrograms per day) was found in this sample. This is at least twice as high as the accepted upper limit of normal.

c. Urinary Urorosein-like Pitments.

Urorosein is a red compound formed in strong acid solution by the oxidation of indolacetic acid. Its exact clinical significance is unknown, but its excretion appears to be most commonly associated with dietary deficiency[91]. Like kynuremic acid which is excreted in increased amount by irradiated dogs (see Part I), indolacetic a acid is derived from tryptophane. The ororosein was determined both with and without $KNO_2$ oxidation. Increased absorption at about 540 mu, character-

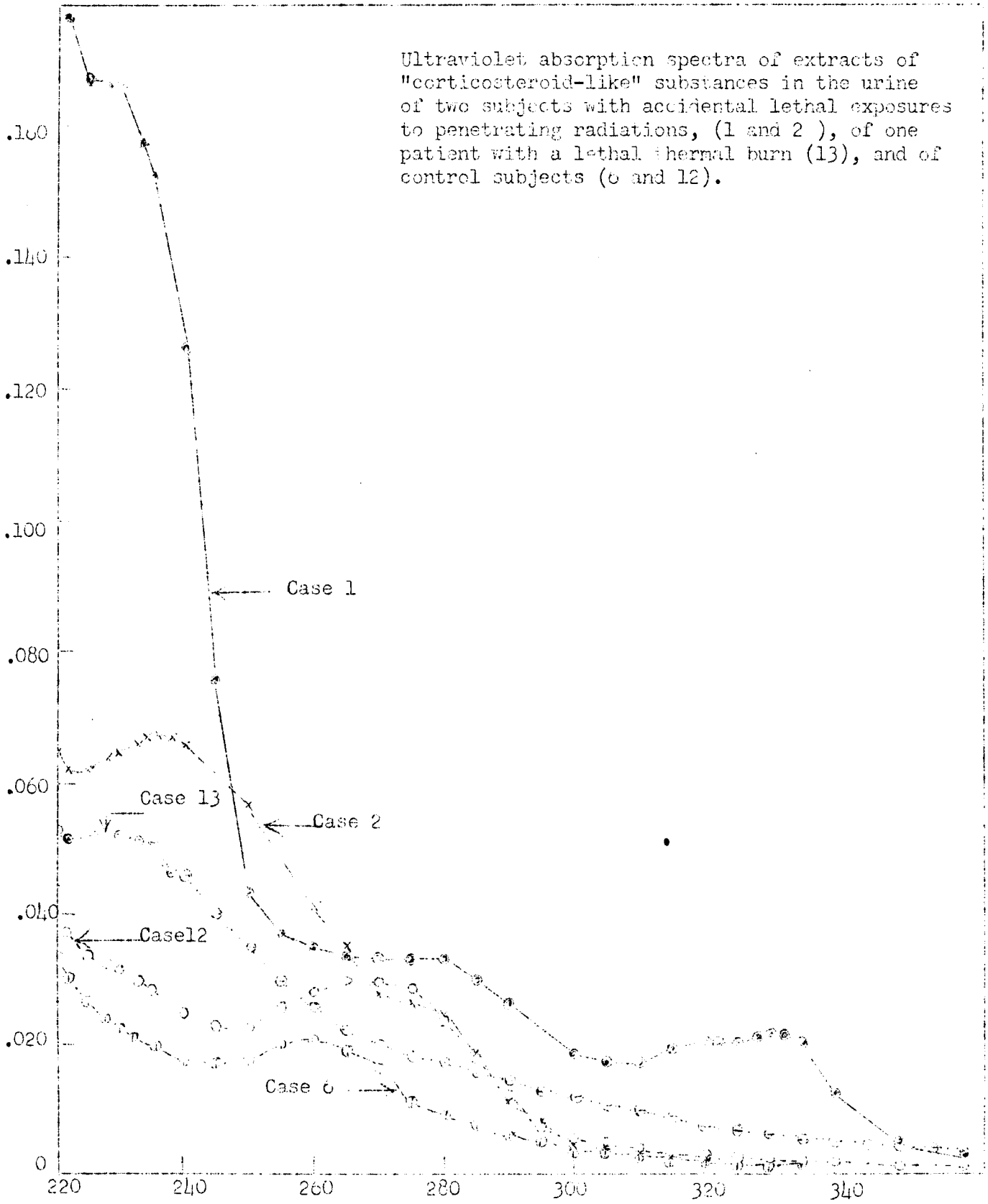

Ultraviolet absorption spectra of extracts of "corticosteroid-like" substances in the urine of two subjects with accidental lethal exposures to penetrating radiations, (1 and 2 ), of one patient with a lethal thermal burn (13), and of control subjects (6 and 12).
.160
.140
.120
.100
.080
.060
.040
.020
0
220
240
260
280
300
320
340
Case 1
Case 13
Case 2
Case12
Case 6
Horizontal- Wave-Length (mu)
Vertical - Extinction per cc of Urine

Fig. 8

istic of urorosein, was found.

d. Liver Function. The serum cephalin cholesterol reaction before death was 3-4 plus. The thymol turbidity was normal. The urinary urobilinogen was not determined. An intense band at 495, however, was seen in the oxidized urorosein fraction. This absorption was most likely due to urobilin.

Cases 2-9.

Death occurred on the 9th day in Case 2. It is estimated that he received a dose of about 900 rep. Cases 6,7,8, and 9 serve essentially as controlls, since their exposures were probably all less than 20 rep.

a. Urinary "Cortico-stercid-like" Substances. Chief emphasis was given the study of the so-called "cortico-steroid-like" substances in these individuals. The spectra from Cases 2,3, 4 and 5 all showed plateaus or actual peaks at about 230 mu similsr to, through not as marked as that found in Case 1. In all instances but one this was greatest 5 to 7 days after the exposure. The relative increase in absorption at 230 mu persisted 1 to 2 weeks in Case 3. In Cases 4 and 5 the values were still abnormal when the study was discontinued 5 and 3 weeks respectively after the exposure. None of the subjects with minimal exposure (Cases 6-9) showed this phenomenon.

Spectra obtained from Cases 2 and 6, as noted previously, are shown in Figure 8.

To illustrate the data more completely, the ratios of total absorption as certain significant wavelengths have been calculated. These ratios, as listed in Table 5, show a clear cut difference between the urine extracts from the individuals with significant radiation exposure and the control subjects. The ratios of the patient with lethal thermal burns are also seen to be similar to those of the subjects with severe radiation exposure.

b. Urinary Coproporphyrin. Case 2 showed the usual terminal increase in total urinary coproporphyrin excretion. (To 451 micrograms per day). The data are summarized in Table 6.

Increased coproporphyrin excretion was found in Case 3 on the third day. A total of 19.8 micrograms per cent, or 332 micrograms per day was excreted on this day. Thirteen other analyses over a period of a month were normal or somewhat elevated (3 values above 150 micrograms per day).

In other cases the per diem excretion of coproporphyrin was normal or depressed. Case 4, for example, had 7 consecutive samples from May 26 to June 4 with concentrations of less than 3 micrograms per cent. Per diem values during this period averaged 52 micrograms per day.

Only 2 determinations of the ratio of the 2 coproporphyrin isomers were done. Seventy-seven per cent of the total porphyrin in Case II from May 26 to May 28 was the type III isomer. In Case III the combined sample from May 21 to June 3 contained about 95 per cent type III coproporphyrin.

Interpretation of the data in all instances is made difficult by the fact that no control analyses had been made on any of the individuals.

c. Urinary Uronilinogen. Abnormal values were found in only Cases II and III. In the former case values rose steadily and reached 6.2 mg per day on May 28-29, the last sample sent us. 6.7 mg. urobilinogen were excreted on May 27-28 and 2.6 mg on June 2-3, by Case III.

The other 45 samples analyzed from Cases III-IX all contained 1 mg. per day or less.

d. "Urorosein" Fraction. Repeated spectra were prepared from the urine of Case II. These showed an increase in absorption at about 490-495 mu which was apparently due chiefly to urobilin. The oxidized fraction showed marked

Table 5

Ultraviolet Absorption Ratios of "Corticosteroid" Fraction from Urine of Los Alamos Personnel and Control Subjects

| Case | Exposure | Date | a 220/240 mu | b 240/260 mu | a/b |
|---|---|---|---|---|---|
| 1. | Lethal Radiation | 3-21-45 | 1.45 | 3.6 | 0.40 |
| 2. | Lethal Radiation | 5-21/22-46 | 1.28 | 1.36 | 0.94 |
| | | 5-22-46 | 1.47 | 1.17 | 1.25 |
| | | 5-26/27-46 | 0.93 | 1.62 | 0.57 |
| | | 5-27/28-46 | 1.09 | 1.40 | 0.78 |
| | | 5-28/29-46 | 1.70 | 1.18 | 1.44 |
| 3. | "Severe" Radiation | 5-22/23-46 | 1.40 | 1.32 | 1.06 |
| | | 5-26/27-46 | 1.40 | 1.75 | 0.80 |
| | | 5-27/28-46 | 1.07 | 1.95 | 0.55 |
| | | 5-30/31-46 | 1.43 | 1.58 | 0.90 |
| | | 5-31/6-1-46 | 1.91 | 1.52 | 1.25 |
| | | 6-9-46 | 1.62 | 1.06 | 1.53 |
| | | 6-12/13-46 | 1.49 | 1.15 | 1.30 |
| 4. | "Severe" Radiation | 5/21-46 | 1.40 | 1.53 | 0.92 |
| | | 5-21/22-46 | 0.78 | 2.86 | 0.27 |
| | | 5-27/28-46 | 1.31 | 1.72 | 0.76 |
| | | 5-28/29-46 | 1.31 | 1.72 | 0.76 |
| | | 5-29/30-46 | 1.29 | 1.73 | 0.75 |
| | | 6-21-46 | 1.40 | 1.50 | 0.93 |
| | | 6-27-46 | 1.37 | 1.67 | 0.82 |
| 5. | "Severe" Radiation | 5-27/28-46 | 0.92 | 2.63 | 0.35 |
| | | 6-9-46 | 1.43 | 1.59 | 0.90 |
| | | 6-11/12-46 | 1.32 | 1.87 | 0.71 |
| 6. | "Light" Radiation | 5-21/22-46 | 1.88 | 0.85 | 2.21 |
| 7. | "Light" Radiation | 5-21/22-46 | 1.88 | 1.08 | 1.74 |
| 8. | "Light" Radiation | 5-21/22-46 | 1.97 | 1.07 | 1.84 |
| 9. | "Light" Radiation | 5-21/22-46 | 1.72 | 0.98 | 1.76 |
| 10. | Control | | 1.69 | 0.97 | 1.74 |
| 11. | Control | | 1.55 | 1.08 | 1.44 |
| 12. | Controls | | 1.60 | 0.89 | 1.80 |
| 13. | Lethal Thermal Burn | 6-5-46 | 1.15 | 1.77 | 0.65 |
| | | 6-8-46 | 1.38 | 1.33 | 1.04 |

Table 6

Urinary Coproporphyrin Excretion in a Case of Acute Lethal Over-exposure to External Radiation. Case 2)

| Date | Urine | Coproporphyrin Excretion | |
|---|---|---|---|
| | vol. (ml.) | micrograms % | micrograms/day |
| 5-21/22 | 310 | 1.8 | 6 |
| 5-22 (12 hrs.) | 500 | 2.4 | 24 |
| 5-26/27 | 990 | 18.8 | 186 |
| 5-27/28 | 1770 | 25.5 | 451 |
| 5-28/29 | (466+) | 25.1 | (117+) |

increase in absorption at about 540 mu immediately after the exposure and again before death.

e. Fecal Porphyrins. No definitely significant trends were observed. Coproporphyrin concentration ranged in most cases from 100 to 300 micrograms per cent.

B. Studies of Hospitalized Patients Given Total Body X-ray

Six hospitalized patients were given a total effective dose of 75 to 310 r (skin) of 200 KV x-rays to total body in divided doses. The therapy was given to 3 patients for neoplastic disease, to 2 patients for partially controlled polycythemia with elevated leucocyte counts and to 1 patient for chronic arthritis.

The details of the treatment will be described in the Plutonium Project Record, but briefly stated they are 200 KV with a half value layer of 1.5 mm Cu, (usually) 3.55 r/minute measured on the skin. The anterior surface of the body was covered by 2 fields and the posterior by 2 fields. Each surface was assumed to receive what each field received, but the "total body dose" was a sum of that received by the anterior and posterior surfaces.

Case I. Most complete studies were made of a 58 year old female (M.G.) who received a total dose of 310 r x-ray to the surface of the body over a period of 18 days. The parotid tumor for which she was treated was first noted in 1929. It was excised in 1934, and again in 1939, 1941 and 1944. Radiation therapy (dose unknown) was given following the first excision. At the time of surgery in April, 1944, the tumor had reached "volley ball" size. Pulmonary metastases were believed to be present. The patient had suffered a 40 pound weight loss during the preceding 18 months.

Treatment was divided into a series of almost daily doses of 20 to 25 r total body x-ray. This was discontinued on the nineteenth day. Supportive therapy included vitamins B and C, feosol, barbiturates, aspirin, and morphine. The latter were given before, during, and after the x-ray therapy.

a. Hematology.

The most striking hematological effect of the treatment was a pronounced shift to the left in the Arneth count, with an increase on about the fifth day in the ratio of 1 and 2 lobed polymorphonuclear cells as compared to 4 and 5 lobed cells. The lymphocyte count fell gradually, while the polymorphonuclear cells decreased abruptly on about the

twenty-fifth day. The platelet count fell temporarily at the end of the first week, rose, and then fell again 2 weeks later.

Erythrocyte sedimentation was already increased before therapy was begun. Eight control determinations ranged from 40 to 50 mm in 1 hour. After treatment most values ranged from 50 to 57 mm in 1 hour.

b. Urine Chemistry.

Marked increases were found during the last week or two in excretion of urinary coproporphyrin, urobilinogen, and urorosein-like pigments. The latter substances were not determined during the early radiation period. The data are summarized in Figure 9.

c. Blood Chemistry

(1) White blood cell chemistry.

These studies were stimulated largely by the report by Abels et al[25] of an increase in acid-soluble phosphorus in white blood cells of leukemia patients given subtherapeutic doses of x-ray.

Two methods devised for the quantitative isolation of morphologically intact white cells from venous blood free of other cellular elements have been described elsewhere[69-70]. Since these chemical studies were done before development of the gramicidin-lysolecithin method, only saponin treated cells were used in these studies.

Details of the analytical procedures used and experimental results obtained will be described elsewhere[44]. Analyses included the determination of phosphorus, ribose, desocyribose and ultraviolet absorption spectra in various extract fractions of these white blood cells in most of the patients studied.

A prolonged increase of several hundred per cent was found in the concentration of phosphorus in the "adenosine triphosphate" fraction of the white blood cells. This increase appeared before any hematological changes were apparent. The data, summarized in Figure 10 are given in terms of both total phosphorus per million white blood cells and the ratio of this fraction to total acid soluble phosphorus. The latter is included to indicate the relatively specific nature of the increase.

Results of analyses of the various white blood cell fractions are summarized in Table 7. No attempt was made in this study to further fractionate the nucleoprotein and lipoid soluble compounds. Neither were pentose or ultraviolet absorption studies made.

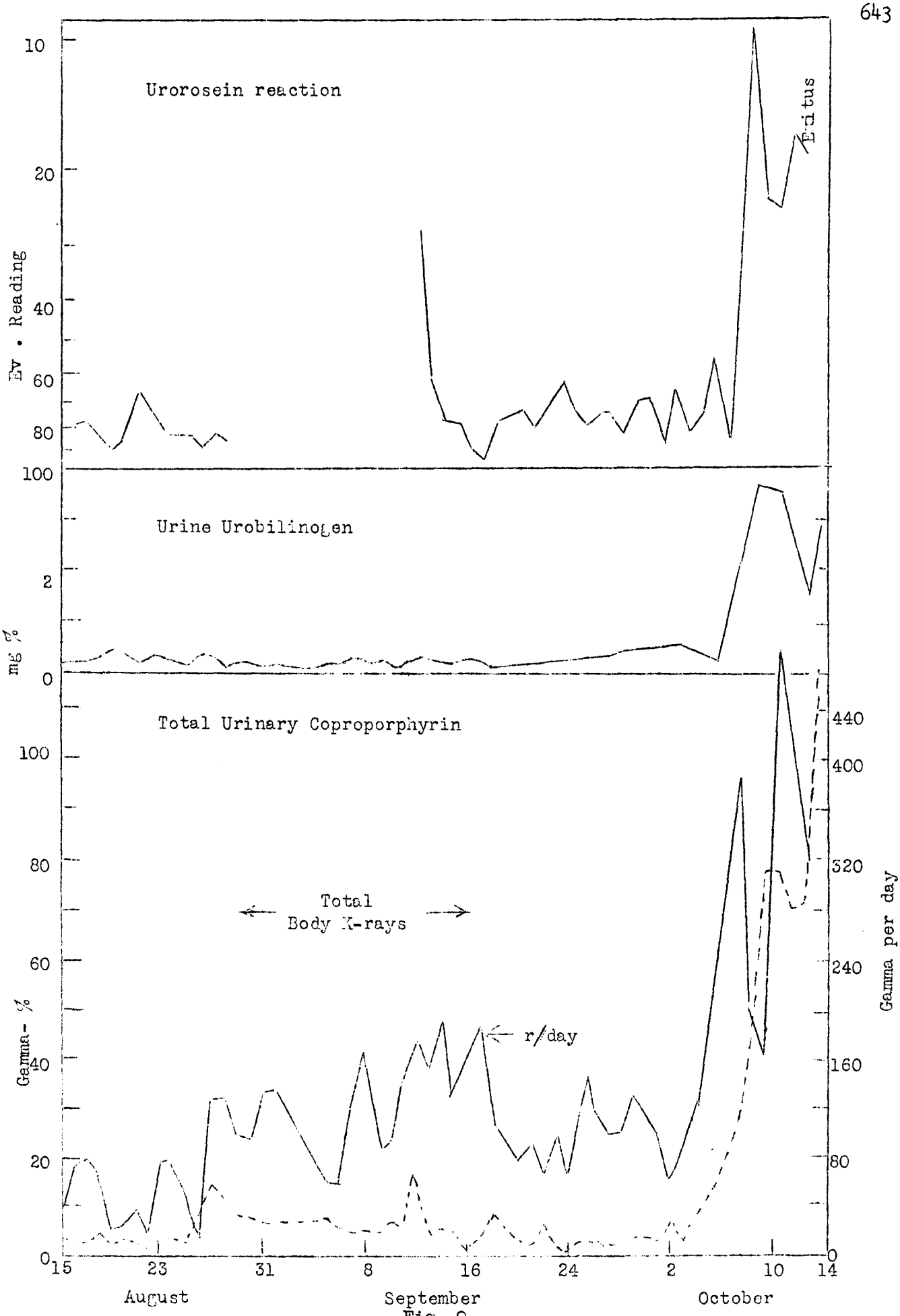
Case II.

A 41 year old male with a metastasizing gastric carcinoma was given a total body dose of 105 r (skin) in 15 doses of 7 r each over a 20 day period. He died at the end of this period.

The most striking biochemical change found was an increase of several hundred per cent in the urinary excretion of urorosein-like pigments. This was most marked in the oxidized fraction. Unlike Case I, the excretion of these compounds returned to the normal range before death. The data are summarized in Figure 11.

Case III, a 73 year old male who was given a total (skin) dose of 226 r total body x-ray over a period of 2 days for treatment of a squamous cell carcinoma of the hand showed a striking increase in the urinary excretion of urorosein.

The chief finding in Case IV was an increase in erythrocyte sedimentation rate starting about 3 weeks after administration of 150 r total body x-ray over a 1 week period. Values rose from control levels of less than 3 mm/hr. to 47 mm/hr. and remained elevated for over 2 months. This patient had polycythemia vera. The hematocrit, which started at 45 per cent, fell less than 5 per cent during the period of study. No significant changes were noted in liver function or porphyrin


Urorosein reaction
Ev • Reading
Titus
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20
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mg %
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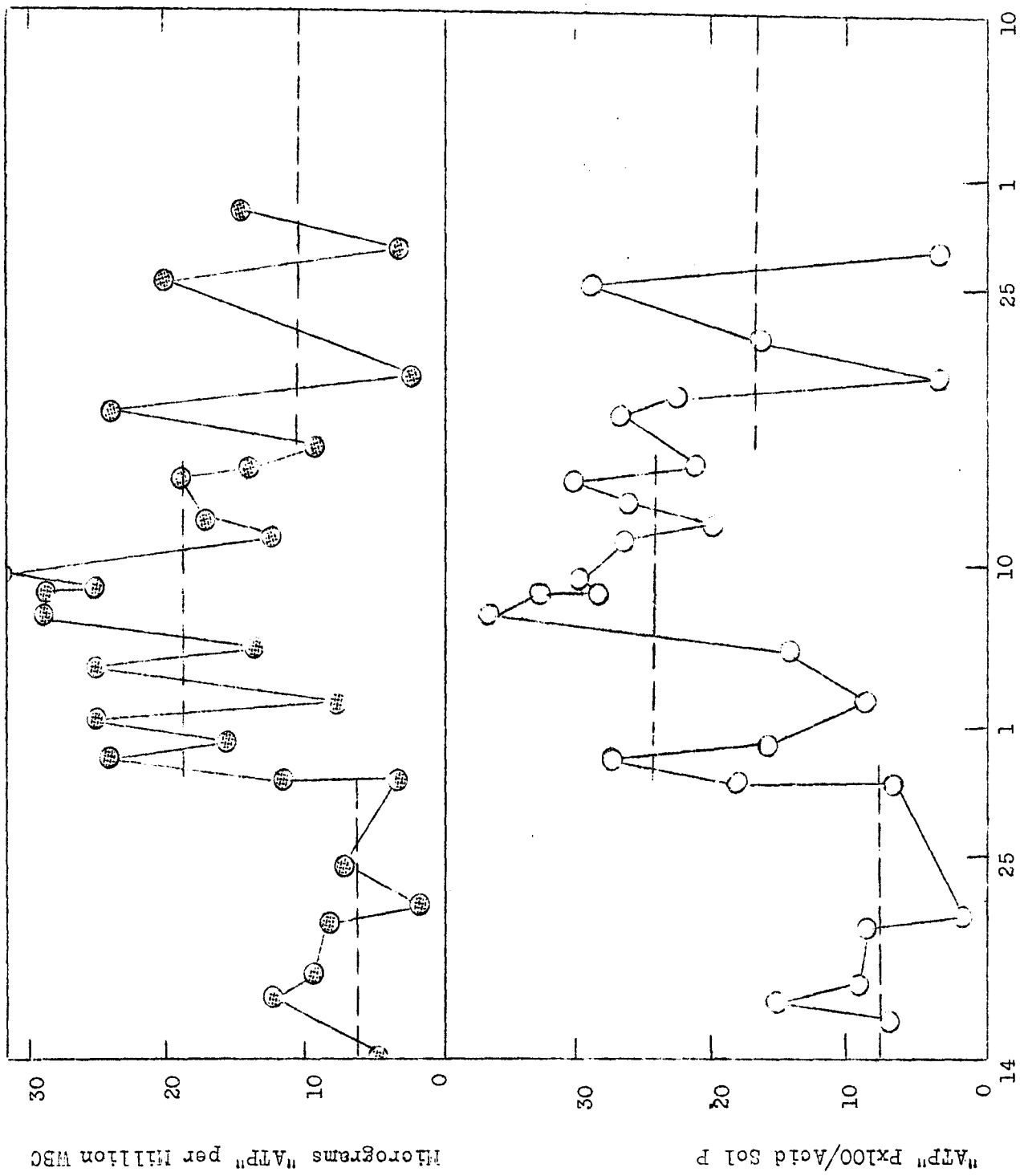
100
80
60
40
20
0
Total
Body X-rays
r/day
Gamma - %
Gamma per day
440
400
320
240
160
80
0
15
23
31
8
16
24
2
10
14
August
September
October

Fig. 9


Micrograms "ATP" per Million WBC
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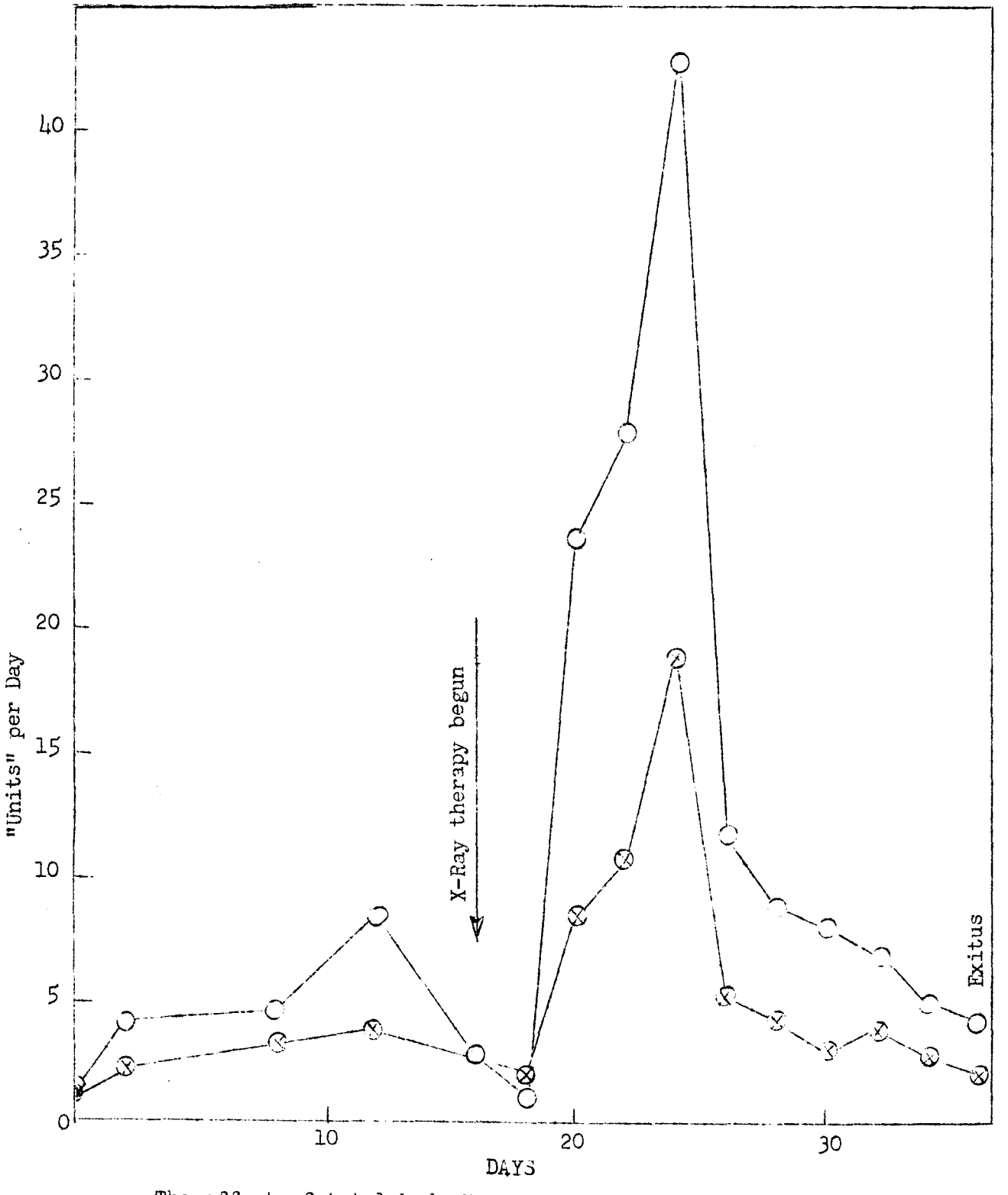
October

Fig. 10




The effect of total body X-ray on the Urinary excretion of urorosein and other urinary pigments in a patient with a metastasizing gastric carcinoma.

**Fig. 11**

Table 7

White Blood Cell Phosphorus Fractions in a Patient Receiving 20-25 r Total Body X-ray Almost Daily. (Total Skin Dose: 310 r)

| | Control period (8 analyses) | Radiation Period (15 analyses) | Post-Radiation period (6 analyses) |
|---|---|---|---|
| Total Phosphorus | 2.18* | 2.66 | 2.19 |
| "Nucleoprotein" plus 'Lipoid" P | 1.46 | 1.90 | 1.50 |
| Acid soluble P | 0.76 | 0.76 | 0.64 |
| "Adenosinetriphosphate" P | 0.06 | 0.19 | 0.11 |
| $\frac{\text{"ATP" P x 100}}{\text{Acid soluble P}}$ | 7.9 | 24.2 | 17.0 |
| "Hexosediphosphate" plus "Phosphopyruvate" P | 0.08 | 0.07 | 0.04 |
| "Inorganic" P | 0.20 | 0.17 | 0.13 |
| Total WBC per cu. mm. | 8300 | 7244 | 2500 |

* Average values are given in terms of micrograms phosphorus per million white blood cells. Total phosphorus is not equal to the sum of the nucleo-protein - lipoid phosphorus plus acid soluble P in these average values since one or the other of these determinations was not done in every instance.

- - -

excretion.

A (skin) dose of 30 r total body x-ray was given to 4 volunteer members of our group. One received daily doses of 2 r, while the others received 3 doses of 10 r each. Chief emphasis was given the study of white blood cell phosphorus in these cases. Such changes as were found in some individuals (i.e., in adenosine triphosphate of the white blood cells) were not consistently present in all four.

C. Studies of Patients with Polycythemia Vera Given $P^{32}$.

Five patients with polycythemia vera were each given a total dose of 20 to 36 mc $P^{32}$ orally over a period of 1 to 5 weeks. All were ambulatory.

In 2 patients, the sedimentation rate reached peak values of 23 and 40 mm in 1 hour respectively. Twelve control values in these 2 patients were all under 2 mm in 1 hour. In both cases, however, the hematocrit fell from control levels of 55-64 per cent to 37 and 40 per cent respectively. No change in either hematocrit or sedimentation rate was found in one patient, while in another the hematocrit fell from 75 to 57 per cent with no change in sedimentation rate.

No significant changes were found in liver function as determined by either serum cephalin cholesterol and colloidal gold tests, or by urinary urobilinogen determinations.

As pointed out elsewhere[46], erythrocyte protoporphyria concentration was not significantly affected by the treatment. Some correlation was found between the protoporphyrin levels and the

color index. As might be expected, highest values were found associated with low color indices.

The urinary coproporphyrin concentrations were unusually low both before and after treatment. Since only "spot" samples of urine were available for analysis, no per diem values could be obtained.

In most instances analyses were made of only total phosphorus and acid-soluble phosphorus in the white blood cells. In all, the average value of the acid-soluble P fell after treatment. The overall average of 28 control determinations was 0.80 micrograms phosphorus per million cells, while the average of 89 analyses after treatment started was 0.66 micrograms per million cells. Possibly significant increases in the "adenoseine triphosphate" fraction were seen in a few instances. These data will be discussed in greater detail elsewhere[44].

### The Effect of $P^{32}$ on Hemoglobin Metabolism in Patients with Polycythemia Rubra Vera

A forty-six year old white female* received a total of 19.8 mc of $P^{32}$ from October, 1944 to June, 1945. Ten mc of this amount was administered intravenously on June 9 and 11, 1945. Her hemoglobin on June 12 was 16.2 grams per cent. By July 31 it had fallen to 12.5 with a red count of 5.7 million. Twenty-eight days later it was 8.6 grams, and by October 2 had come down to 6.7 grams with a red count of 2.66 million. Unfortunately no reticulocyte determinations were done until September 27. From this date until October 13 the latter ranged from 3.6 to 8.5 per cent. During this period fecal urobilinogen excretion was two to three times above normal. The bone marrow (biopsy) exhibited a marked normoblastic hyperplasia. Pertinent studies are plotted in Figure 12.

From the data above it is obvious that the patient developed a hemolytic anemia following the final $P^{32}$ administration. This is shown by the elevated fecal urobilinogen excretion as well as by the rapid fall in hemoglobin concentration despite an elevated reticulocyte count. No blood transfusions were given during the period of study.

Hemoglobin and reticulocyte studies were made in three other patients who received oral $P^{32}$ therapy. There was no indication from the reticulocyte counts of sufficient suppression of erythropoietic activity to account for the hemoglobin fall in these patients. Actually at least one of them (W.B.) had a definitely elevated reticulocyte count during part of the period of hemoglobin fall. The hemoglobin concentration in other patient (A.O.) was 12 grams. Following the administration of 18.6 mc $P^{32}$ over a period of 24 days, his hemoglobin rose steadily to about 17 grams. This study is important because it indicates that normal erythropoiesis may follow the administration of this dose of $P^{32}$. Unfortunately, however, the absence of bile pigment excretion studies in these patients makes it impossible to prove with certainty the presence of a hemolytic reaction.

### D. Studies of Manhattan Project Personnel

A number of biochemical studies were made of personnel at the Argonne National Laboratory, Chicago, and at Iowa State University, Ames, Iowa. Exposures were chiefly to various metals, especially uranium and to chemicals. Radiation exposure was minimal and always combined with chemical and/or metal exposure.

No consistent changes were observed which could be attributed specifically to the radiation exposure. Studies dealing with the effects of metal exposure have been described elsewhere[39,71-72].

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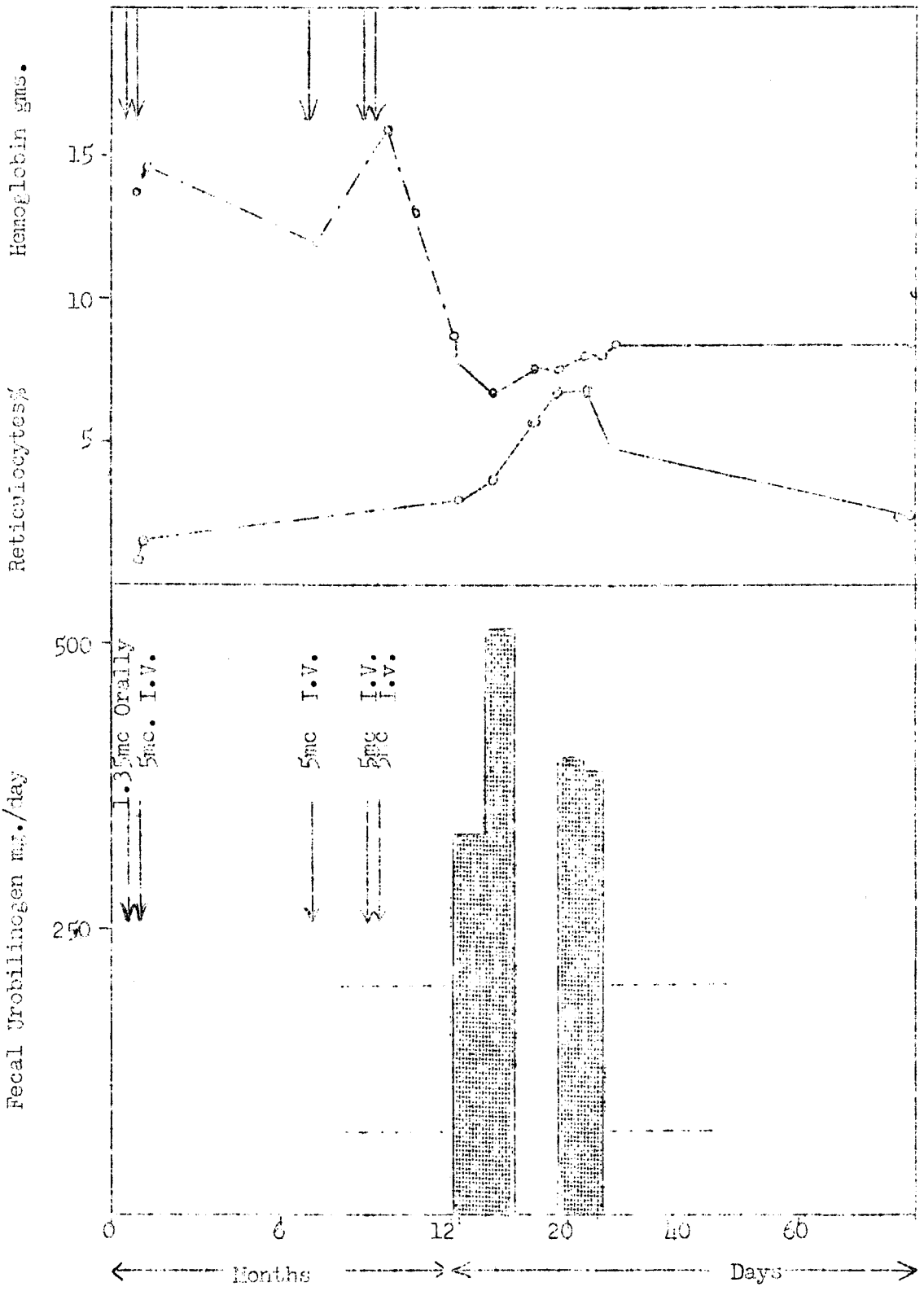
* We are indebted to Dr. C. J. Watson and Miss V. Hawkinson of the Department of Medicine, University of Minnesota, for the studies on this patient.




The Effect of $P^{32}$ on Hemoglobin Metabolism in a Patient with Polycythemia
(M. K.)

Fig. 12

## E. Discussion

### General Considerations

In reviewing the literature on the biochemical effects of radiation, one is struck by the unusual amount of conflicting data presented; almost every blood and urinary constituent studied has been reported variously as elevated, depressed, or unchanged. The reason for this variance is to be found largely in the wide range of experimental conditions, involving differences in type of radiation, total dose, dose rate, amount of body exposed, clinical status of subject at time of radiation, and time of analysis after radiation. Thus, for example, Jacobs and Motojima[27] report blood cholesterol concentration to be elevated in irradiated patients with carcinoma who are in relatively good clinical condition, whereas it is depressed in cachectic patients. Many reactions are reported to vary as a function of time after radiation. This is illustrated, for example, by studies of alkali reserve which indicate that a transitory acidosis may occur after radiation followed by alkalosis for several days, and then a return of acidosis in the terminal period.

In general the limiting factor in these studies appears to be the fact that the reactions studied are those which appear as a result of a long chain of interrelated responses; attempts to study more fundamental reactions are relatively few. The studies of Fricke[4] and others[2] on the chemical effects of radiation, of Mitchell[12-14] on nucleic acid metabolism, and of Dale[73] and Barron and others[74] on enzyme metabolism are among the exceptions to this statement. The increased availability of tracer elements should give great impetus to studies of rates of turnover of numerous substances affected by radiation. These should give us a much more dynamic view of the problems involved.

While the most immediate concern of our studies was the development of tests which might prove of diagnostic and prognostic value in over-exposed human subjects, the ultimate value of such studies must lie chiefly in the better understanding they might afford of the nature of radiation effect. Such understanding might then lead to more rational therapeutic measures for over-exposure, and possibly to a better understanding of such allied fields as cancer and its treatment.

### Possible Interpretations of Presented Data

At the outset it should be emphasized that considerable more study is necessary for the proper interpretation of the experimental data presented in the previous section. Certain possible correlations, however, are suggested by the literature.

a. "Corticosteroid-like" substances

Plasencia[6] has emphasized certain similarities between radiation toxicity and hypofunction of the adrenals as seen in Addison's disease. These include depression of serum sodium and cholesterol, instability of blood sugar with a tendency to hypoglycemia, and a tendency to hypotension common to both conditions. On the other hand, certain similarities exist between thermal and radiation burns. In the former condition Talbot et al[66] have shown that "corticosteroid" excretion is similar to that in conditions with hyperfunction of the adrenal cortex. Unfortunately, no data was presented on the progressive changes found.

In irradiated subjects, the increase in specific absorption at about 230 mu in urinary "corticosteroid" extracts was the most consistently significant abnormality found by us. In the two instances where repeated analyses were made before death there was a terminal drop in the excretion of the substance responsible for this absorption. In one of these instances (Case 13), death was due to thermal burns. This would suggest an early hyperfunction of the adrenals followed by a terminal tendency to hypofunction.

As noted previously, time has not per-

mitted adequate study of this phenomenon. The identity of the 230 mu absorbing compound should be further investigated by study of its reactions, solubilities, and infra-red spectrum at least.

b. Urorosein and other Urinary Pigments

The most marked increases in excretion of urinary pigments were observed in the three patients who were ill at the time of radiation therapy was given. Relatively slight changes only were found in the 2 previously healthy individuals who were accidentally exposed to lethal doses of radiation.

Several observations have been made which might conceivably be due to mechanisms similar to those relating to urorosein excretion:

(1) A terminal increase has been found in the excretion of kynurenic acid by dogs given a lethal exposure to total body X-radiation[41,42] Like indoleacetic acid, a precursor of urorosein, kynurenic acid is derived from tryptophane. (Little if any, indoleacetic acid appears to be excreted by dogs.) It seems, therefore, that a disturbance in tryptophane catabolism may be produced in both species by excessive radiation exposure.

(2) The inactivation of auxin (indoleacetic acid) by x-irradiation has been described by Skoog[75]. He suggests that inhibition of growth of plants may be due to this factor.

(3) Macht[76,77] has described an inhibition of lupinus allus growth on addition of serum from individuals exposed to even very small amounts of x-rays. These studies have not, to our knowledge been repeated. While the relationship here is especially tenuous, one wonders whether such an effect could conceivably be due to the presence of an altered indoleacetic acid or similar compounds in these sera.

(4) Stenstrom and Lohmann[78] have reported the chemical alteration if tryptophane itself following exposure to x-irradiation.

Graham[79] has reported the increased excretion of urine pigments (which he erroneously identified as coproporphyrin) in several irradiated patients. Watson and Layne[80], on the other hand, found no significant increase in urorosein excretion in patients with carcinoma of the cervix following x-ray therapy (local).

## Summary and Conclusions

From the above experimental studies and from a survey of the literature, the following conclusions have been drawn:

1. The most striking biochemical changes found after excessive radiation exposure in humans were (1) an increase in urine "corticosteroid-like" substances in all of the 5 individuals studied, (2) a prolonged increase in the "adenosine triphosphate" phosphorous in the peripheral white blood cells of a patient given total body x-ray for the treatment of a metastasizing parotid tumor, (3) pronounced terminal increases in urinary coproporphyrin excretion in 3 patients who died within a few weeks after heavy exposure to external radiations, and (4) increased excretion of "urorosein fraction" pigments in severely ill patients given large doses of total body x-irradiation. Other changes found included a shift to the left in the Arneth count, and an increase in erythrocyte sedimentation rate.

2. The chief changes found in experimental animals include the following: (1) a drop in urinary coproporphyrin excretion followed by a terminal rise, (2) an increased excretion of fecal urobilinogen, indicative of increased red cell destruction, (3) an increased terminal excretion of kynurenic acid, (4) an increased excretion of uric acid and a decreased uricolytic index, and (5) terminal increases in excretion of urinary urobilinogen.

3. More fundamental information is needed on the nature of both early and late biochemical effects of radiation. Studies of physiologically important

oxidation-reduction phenomena, and protein and enzyme effects seem especially promising.

Acknowledgments

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## III. MEDICAL SCHOOL NEWS

### Journal-Lancet Lecture

Dr. L. J. Witts, Nuffield Professor of Clinical Medicine at Oxford University, will deliver the annual Journal-Lancet Lecture on Wednesday, June 8, at 3:00 p.m. in Todd Amphitheater, University Hospital. Dr. Witts' subject will be "Intestinal Macrocytic Anemia."

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### Special Lecture

Dr. Herman Taylor of London Hospital, London, England, will be visiting our campus next week. Members of the Medical School staff and physicians of the Twin Cities will have an opportunity to hear Dr. Taylor speak on the subject, "Non-Operative Treatment of Perforated Ulcer," on June 9 at 4:00 p.m. in Todd Amphitheater.

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### Continuation Course in Cancer

Dr. Lauren Ackerman of the Department of Surgery, Washington University Medical School, St. Louis, delivered a special lecture on Thursday, June 2, on the Medical School campus. Dr. Ackerman who came to participate in a course in Cancer Control being offered for physicians of Minnesota and North Dakota spoke on the subject of "Malignant Melanoma of the Skin."

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### Coming Events

Friday, June 17 - 12:00 noon - Dr. Clyde Butler, Surgeon to the London Hospital, "Penicillin Therapy in Osteomyelitis and Hand Infections", Powell Hall Amph. Luncheon will be served.

### Biographical Briefs -- Pharmacology

Dr. Raymond N. Bieter was born at Heron Lake, Minnesota. His early schooling including high school was received in this same community in southwestern Minnesota. He came to St. Paul in 1917 to begin his premedical studies at St. Thomas College. In 1919 Raymond entered the University of Minnesota Medical School, and he received his M.D. degree in 1924.

He began graduate studies in Pharmacology here under Professor Arthur Hirschfelder and was made an instructor in Pharmacology in 1925. He continued his investigative work in Pharmacology and in 1929 received his Ph.D. degree with a major in Pharmacology and a minor in Physiology and Internal Medicine. Dr. Bieter's Ph.D. thesis was concerned with the physiology and pharmacology of the kidney.

Dr. Bieter has been active in the Department of Pharmacology here at the University of Minnesota since 1924 except for the year 1930-31. This period he spent as an associate in Physiology at Johns Hopkins University School of Medicine. During this year in Baltimore, Dr. Bieter worked under Dr. E. K. Marshall, Jr. He resumed his teaching and research activities as an Associate Professor of Pharmacology in this institution in 1931 and was made full Professor in 1940. He was named Head of the Department of Pharmacology in 1943.

Dr. Bieter served as Visiting Professor of Pharmacology at the University of Chicago in the summer of 1941. Since 1938, he has collaborated with the Bureau of Plant Industry of the U.S. Department of Agriculture. During the war years, he carried out investigative work for the Office of Scientific Research and Development. He has since the war been conducting scientific studies for the Army.