ORINS-25

BIOLOGY AND MEDICINE

UNITED STATES ATOMIC ENERGY COMMISSION

THE ACUTE RADIATION SYNDROME

A Medical Report on the Y-12 Accident
June 16, 1958

Compiled by
Marshall Brucer

April 1959

Oak Ridge Institute of Nuclear Studies, Inc.
Oak Ridge, Tennessee

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From the Medical Division
Oak Ridge Institute of Nuclear Studies
Oak Ridge, Tennessee
Under contract with the United States
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The physical and engineering description of the events leading to the Y-12 radiation accident of June 16, 1958, are reported in detail in Y-1234.*

The medical report of the acute period of hospital care during the six weeks immediately after the accident is being submitted as a U. S. Atomic Energy Commission Report, ORINS-25. Much of the laboratory work is unfinished and the very important follow-up studies may not be available until many years have passed. Many detailed reports of laboratory analyses are being prepared and summaries of various phases will be published in recognized medical journals.

This report of the acute phase of the medical therapy is distributed because of the recognized and necessary interest of many persons involved in radiation safety and in the treatment of future patients. A few items of personal history of no radiation interest have purposely been omitted from the published clinical record. As is true of all medical documents, there is no security classification on this document. It is freely available to any physician and to nonphysicians who have a necessary interest in radiation. Nevertheless, the clinical portions are a medical record and as such should be recognized as a privileged communication.

M. Brucer, M.D.
Chairman, The Medical Division
Oak Ridge Institute of Nuclear
Studies

* Accidental Radiation Excursion at the Y-12 Plant, June 16, 1958. U. S. Atomic Energy Commission Report Y-1234, July 28, 1958.

This material has been presented verbally and in preliminary publications to the following groups:

August 8, 1958	Interim report published	Brucer
August 25, 1958	Medical consultants of ORINS	Brucer, Sitterson, Andrews, Kretchmar
August 27, 1958	Industrial physicians of AEC	Brucer, Sitterson, Andrews, Kretchmar
October 9-10, 1958	Sandia Army Medical Officers Course	Brucer
October 28, 1958	AEC Biomedical Directors	Brucer
October 28, 1958	Roane County Medical Society	Andrews, Kretchmar, Sitterson
October 31, 1958	Maxwell AFB, Air University, Medical Officers Course	Brucer
November 4, 1958	Medical staff of ORINS	Brucer, Sitterson, Andrews, Kretchmar
November 14, 1958	Navy Nurses' Course in Nuclear Medicine, Bethesda	Palmer
November 21, 1958	Kansas City Academy of Medicine (Submitted for publication December 30, 1958)	Brucer
December 22, 1958	Meeting on Management of Radiation Accidents, called by Dr. Bruner (AEC) and Dr. Zubrod (NIH) in Washington	Andrews, Sitterson
January 7, 1959	San Francisco, Naval Medical Officers Course	Brucer
January 13-16, 1959	Paris meeting, Curie Foundation	Andrews
February 14, 1959	ORINS Board of Directors	Brucer, Andrews, Sitterson, Ross, Kretchmar, Kyker
February 16, 1959	Georgia Tech reactor meeting	Sitterson

February 19, 1959	Meeting on Diagnosis of Radiation Injuries called by Dr. Ely and Dr. Beard (AEC) in Washington	Andrews
March 14, 1959	Southwestern Section of the Society of Nuclear Medicine, New Orleans	Andrews, Kretchmar
March 16, 1959	Medical Staff, University of Iowa	Brucer
March 20, 1959	Sandia Army Medical Officers Course	Brucer
April 2, 1959	Sophomore Class, Temple University Medical School, Philadelphia	Andrews
April 3, 1959	School of Aviation Medicine, Gunter AFB	Brucer

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CLINICAL REPORT

Beecher W. Sitterson, M.D.

Introduction

This section of the report deals with the events that occurred in connection with the medical care of the patients from the accident at the Y-12 Plant of the Union Carbide Nuclear Company (UCNC) on June 16, 1958. Only the period of hospital care is covered. First, a general account is given. This is not limited to medical developments, but attempts to describe the events in the total experience just as they occurred. Next, the medical developments of a clinical nature are described. Details of the results of serial hematological and biochemical studies are not included because they are reported in separate sections. Last, individual case reports are given.

General Report

At about 11:00 p.m. on June 16, 1958, the clinical staff of the Medical Division of the Oak Ridge Institute of Nuclear Studies (ORINS) was advised that an accident had occurred at the Y-12 Plant (about 2:00 p.m.) in which five men had received large, and probably dangerous, doses of radiation. The Union Carbide Nuclear Company requested that these men be admitted to the Medical Division Hospital for treatment and observation. Regular bed space was not available and it was necessary to convert a patients' recreation room into a temporary ward before admitting the men.

The five men, designated as Patients A, B, C, D, and E, were admitted at 1:00 a.m. on June 17, 1958, and placed in the improvised ward. All were ambulatory. They had already received thorough shower baths and a complete change of clothing at the Y-12 Plant. Monitoring over their bodies at skin surface showed maximum activity of 0.3 milliroentgens per hour. Histories of symptoms since the accident, physical examinations, complete blood counts including absolute lymphocyte counts, bone marrow aspirations, and blood samples for

special biochemical studies were obtained on admission. Collections were started for the measurement of 24-hour urine volumes and arrangements were made for the freezing and storing of all urine and stool specimens. No specific therapy was instituted. Admission orders included recording of temperature, pulse rate and respiratory rate every six hours; body weight daily; regular hospital diets; permission to be ambulatory in the ward; chest X rays; throat cultures, with sensitivity studies on any pathogenic bacteria found; daily urine and stool examinations for occult blood.

At 3:00 a.m. Dr. K. Z. Morgan of the Health Physics Division of the Oak Ridge National Laboratory (ORNL) telephoned a tentative estimate of the doses the men had received. The five estimated doses ranged from 320 to 706 rem with the probability of their being not less than one half (and maybe more) than these figures.

The following morning, about eight hours after admission, complete histories were obtained, physical examinations were done, and the names and addresses of relatives who might serve as bone-marrow donors were obtained. One physician was assigned the task of calling these relatives by telephone and asking them to come to Oak Ridge. Excellent cooperation was received even though travel of a few hundred miles was involved in some instances.

Blood typing and cross-matching procedures were done on the relatives, plus numerous other persons who volunteered as donors. Persons compatible in major blood types (relatives if possible) were selected for each patient as possible bone-marrow donors. These potential donors were requested to remain in the Oak Ridge vicinity, until further notice, to be called if needed.

The immediate families of the patients were granted unrestricted visiting privileges but other visitors were not permitted. Nevertheless, large numbers of people came to try to visit or to volunteer as blood donors. It became necessary to arrange a special reception desk to handle them.

In anticipation of a widespread interest in the effects of radiation in human beings, the following blood-chemistry determinations were obtained the first morning, about 18 hours after the radiation exposure: total serum proteins and albumin-globulin ratio; electrophoretic studies of serum proteins; blood urea nitrogen; serum uric acid; fasting blood sugar; total serum cholesterol and cholesterol esters; serum lactic dehydrogenase; serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase; serum sodium, serum potassium, and serum chloride; CO_2 combining power; serum calcium, serum phosphorus, and serum alkaline phosphatase.

Subsequent hematological and biochemical studies were obtained as described in separate sections of the report.

The Medical Division had no facility for whole-body counting of induced radioactivity in these men; however, beginning on the 1st day, an experimental model of a linear scanner was used to obtain a non-quantitative record of the radioactivity present in their bodies.

At 8:00 p.m. on June 17th a conference was held with about 40 participants from Oak Ridge Operations of the Atomic Energy Commission, Union Carbide Nuclear Company (Y-12 and X-10 of ORNL and the Gaseous Diffusion Plant, K-25) and ORINS. Consultants from outside Oak Ridge included Dr. Charles L. Dunham, Division of Biology and Medicine, AEC, Washington; Dr. Louis Hemplemann, University of Rochester; Dr. Eugene Cronkite, Brookhaven National Laboratory; Dr. Victor P. Bond, Brookhaven National Laboratory; and Dr. George Harrell, University of Florida (see Appendix for list). Developments up to that time, dose estimates, further diagnostic procedures, possible therapeutic measures, and other problems related to the care of the patients were discussed. At this conference it was revealed that three additional men were exposed to sizable amounts of radiation in the accident but because they had received much smaller doses, hospital care had not been considered necessary. The medical opinion was that these three men should also be admitted to the hospital for observation. Accordingly, Patients F, G, and H were admitted the following morning, June 18, 1958, and underwent the same procedures and laboratory studies as previously mentioned in connection with the five patients admitted originally.

On the 2nd hospital day it appeared that having all patients together in one ward was undesirable because of psychological factors. Therefore, they were separated and placed in private rooms. This was accomplished by discharging several regular Medical Division research patients who otherwise would have been retained longer and by postponing the scheduled admission of other patients.

On June 18th Dr. Shields Warren, Medical Consultant to the AEC, visited the hospital for consultations on the medical care of the patients.

The use of antibiotics for "prophylactic" purposes was discussed early in the hospital course and it was decided to withhold them unless some specific indication for their use occurred.

During the first three days the question of whether or not to give bone-marrow infusions to any or all of the five patients who had received the highest doses was discussed repeatedly. No specific information was available concerning the optimum time, or maximum permissible delay after radiation for giving bone marrow to human beings in these circumstances. Small-animal experiments seemed to indicate that the delay should not exceed a few days. Therefore, on June 19th the concensus was that a definite decision had to be made.

To arrive at a decision the five patients were classified according to the latest dose estimates, severity of hematological changes, and clinical course. Dose estimates had been received from two separate groups at ORNL, one stated in rads and the other rems, and had been revised downward considerably by this time. To classify the hematological and clinical developments, the patients were graded from 1 to 5, 1 representing most severe, and 5 representing the least. This classification of the patients is shown in Table 1.

Table 1

Patient	Dose Estimates				Hematological Changes Rank Order*	Clinical Course Rank Order*
	Group 1		Group 2			
	rad	Rank Order*	rem	Rank Order*		
A	276	1	320	1	1	1
B	188	4	256	4	3	3
C	230	3	292	2	4	5
D	239	2	272	3	5	4
E	163	5	201	5	2	2

*Rank Order: 1 - most severe; 5 - least severe

The dose estimates from the two groups placed the patients in the same order regarding severity of exposure except for reversal of positions between the two patients receiving the second and third largest doses. The hematological and clinical impressions agreed except for reversal of positions between the two patients ranked fourth and fifth in severity. Still, the order of severity of the dose estimates did not correlate very well with the hematological and clinical data. There was a particular discrepancy in Patient E who was estimated to have received the lowest dose but appeared from the other data to be the second most severely affected.

An attempt, based on all available information, was made to estimate the prognosis of each patient. It was believed that Patients B, C, and D had an excellent chance to survive and Patients A and E probably had better than fifty per cent chance of survival.

The possibility of bone-marrow infusions proving to be harmful was considered. Again there was no specific information concerning this in human beings, but from small-animal studies it appeared that

the doses of radiation received by these patients might be in the range where bone-marrow infusions would increase the mortality.

The possibility of giving bone marrow to Patients A and E only, since they appeared to be the most severely affected, was seriously considered. The decision reached was against giving bone marrow to any of the patients although its use was not ruled out for the future should the condition of any patient become grave enough to warrant the use of any measure offering possible therapeutic value.

The previously selected potential bone-marrow donors were released from the request to remain in the Oak Ridge vicinity after this decision was made.

On June 20th, four days after the accident, a special group conference was held with the patients for the purpose of giving them a full, frank, and complete-as-possible explanation of what had happened and what they might expect. Dr. Robert A. Charpie of ORNL explained how the accident had occurred and the range of the estimated doses they had received. Staff members of the Medical Division explained the medical developments that would probably occur and the estimated time relationships involved. Epilation, bone-marrow depression, and effects on testicular function were discussed. As regards testicular function, it was stated they would not become impotent but probably would go through a period of sterility. The possibility of delayed effects was explained in terms of an increase in statistical odds of certain diseases developing in a large group of people exposed to radiation; but they were told that for any one individual in such a group, no prediction could be made. They were assured that all of them were expected to recover, but some of them might go through a period of danger and that full preparations had been made to treat any dangerous situation that might arise. This conference improved the morale of the patients quite noticeably.

After this conference a special discussion was held individually with the wife of each patient and these medical implications were explained.

On June 26th a complete ophthalmological (including slit lamp) examination was performed on each patient. Later in their course each patient's visual acuity was determined.

After nine days Patients F, G, and H, who received the lowest doses and who had not been admitted until June 18th, had not shown any significant clinical evidence of radiation damage. They were discharged on June 26, 1958, to be observed as outpatients every other day.

After recovering from the nausea and vomiting of the first few days, and except for specific minor incidents, Patients A through E were essentially asymptomatic during the first two weeks in the hospital.

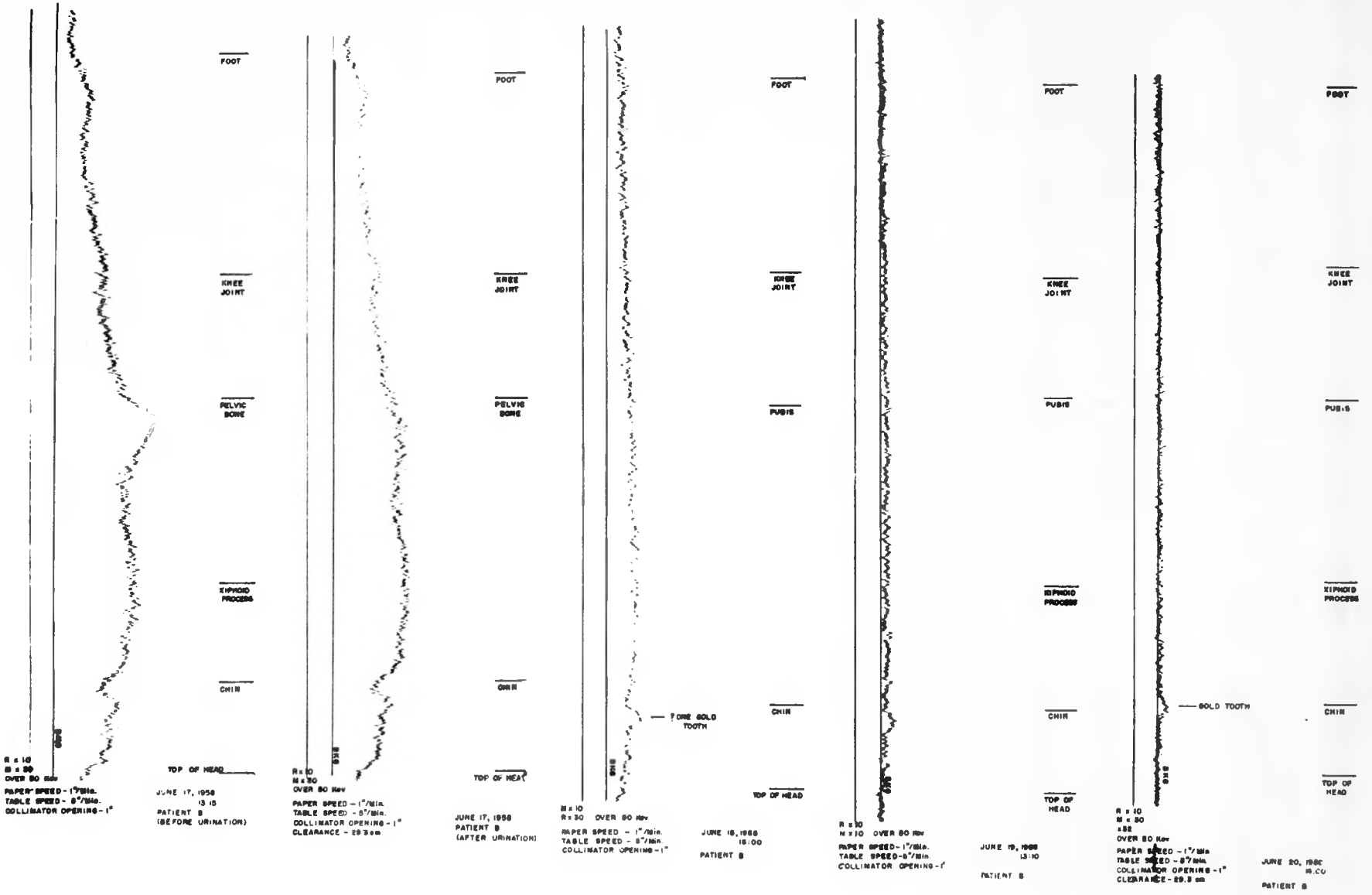


Figure 1. Linear Scan on Patient B

At the end of this time, hospital confinement was becoming intolerable to them. Beginning on July 3rd, they were permitted to leave the hospital to visit their homes from 2:00 p.m. until 10:00 p.m. daily. Arrangements were made to have someone else drive their cars on these trips and they were instructed not to engage in any physical activity greater than what they had been doing in the hospital. This arrangement boosted the morale of the patients greatly and they showed no evidence of ill effects from it. By the 24th hospital day, however, white blood cell counts and blood platelet counts had fallen to levels that were considered dangerous and therefore the daily "passes" were canceled.

During the period of daily "passes" sperm-count studies were initiated. The desirability and importance of these studies were explained to each patient individually, including the three who were outpatients at the time. Nevertheless, participation was left on a voluntary basis. Four patients participated in this initial study.

By the 39th hospital day hematological studies indicated that the patients were in the recovery phase and out of danger of hemorrhage. The daily "passes" were instituted again and continued until the 44th day when, on July 30, 1958, the patients were discharged from the hospital to be observed every other day as outpatients. (Patients F, G, and H returned to work on July 14, four weeks after the accident, and Patients A, B, C, D, and E returned to work on September 8th, 12 weeks after the accident.)

In addition to the studies mentioned previously, samples of urine, blood, and bone marrow were provided to several investigators in other laboratories, at their request, for studies in which they were particularly interested.

The final estimated doses reported by the Health Physics Division of ORNL were as follows: Patient A--365 rads, Patient B--270 rads, Patient C--339 rads, Patient D--327 rads, and Patient E--236 rads.

Clinical Developments

Induced Radioactivity. The linear scanner permits the recording of a profile of radioactivity from the feet to the top of the head. Such recordings on these patients showed profiles resembling human bodies in the supine position, reflecting the general distribution of radioactive material, presumably sodium-24, throughout their bodies (see Fig. 1). Although quantitative information was not obtained in this manner, the relative amounts of remaining radioactivity could be followed by comparing the results of serial studies. Three days after the accident the activity was almost down to background level and on the 4th day only background activity was detected. It was estimated that there

had been about 10 microcuries of sodium-24 in each of the five patients with the highest doses.

Gastrointestinal. Of the five patients receiving the highest doses of radiation, Patients A, B, and D experienced nausea and vomiting with onset ranging from two to four hours after the accident. Patient E became nauseated about five hours after the accident but did not vomit. Patient C had neither nausea nor vomiting. In Patient B the nausea and vomiting persisted during the early morning hours after admission to the hospital. By 8:00 a.m. on June 17th all patients were free of these symptoms, had no recurrence during the day, and ate well at all three meals. During the early morning hours of June 18th Patients A and B, plus Patient E who had experienced nausea but no vomiting previously, had nausea and vomiting. Patient D experienced nausea and vomiting after awakening and Patient C, who previously had experienced neither nausea nor vomiting, had a brief period of nausea after awakening but no vomiting. The psychological effect of observing others with nausea and vomiting was considered as a possible etiological factor in the development of these symptoms in Patients D and C who had had no difficulty before awakening. Therefore, the patients were separated and placed in private rooms. The vomiting subsided in Patients A, B, C, and E on June 18th, but Patient B continued to feel nauseated the following day and Patient A continued to have nausea for three additional days.

Patient D's nausea and vomiting seemed to subside on June 18th also, but later in the day he complained of vague discomfort, without definitive characteristics, in the left scapular region. This persisted and on the following day, June 19th, was described as a "pulling sensation" extending from the midepigastrium through the left part of the chest to the left scapular region. Late in the day he again became nauseated, did not eat the evening meal, and vomited one time. The next morning, June 20th, he remained nauseated, vomited once, and felt quite weak. These symptoms subsided about midday on June 20th and did not recur thereafter. On the 24th day he developed moderately severe pain in the right lower quadrant of the abdomen, without other associated symptoms, elevation in temperature, or significant physical findings. This subsided after about eight hours, without specific therapy. Throughout the remainder of his hospital care he did not complain voluntarily of recurrence, but, when questioned directly, he reported vague intermittent abdominal discomfort.

The vomiting was not severe enough in any of the patients to cause significant disturbance in serum electrolytes. None of the patients had diarrhea.

Fever. Except for elevations in temperature in two of the patients at the time of specific infections, as described later, none of the men had any fever during their hospitalization.

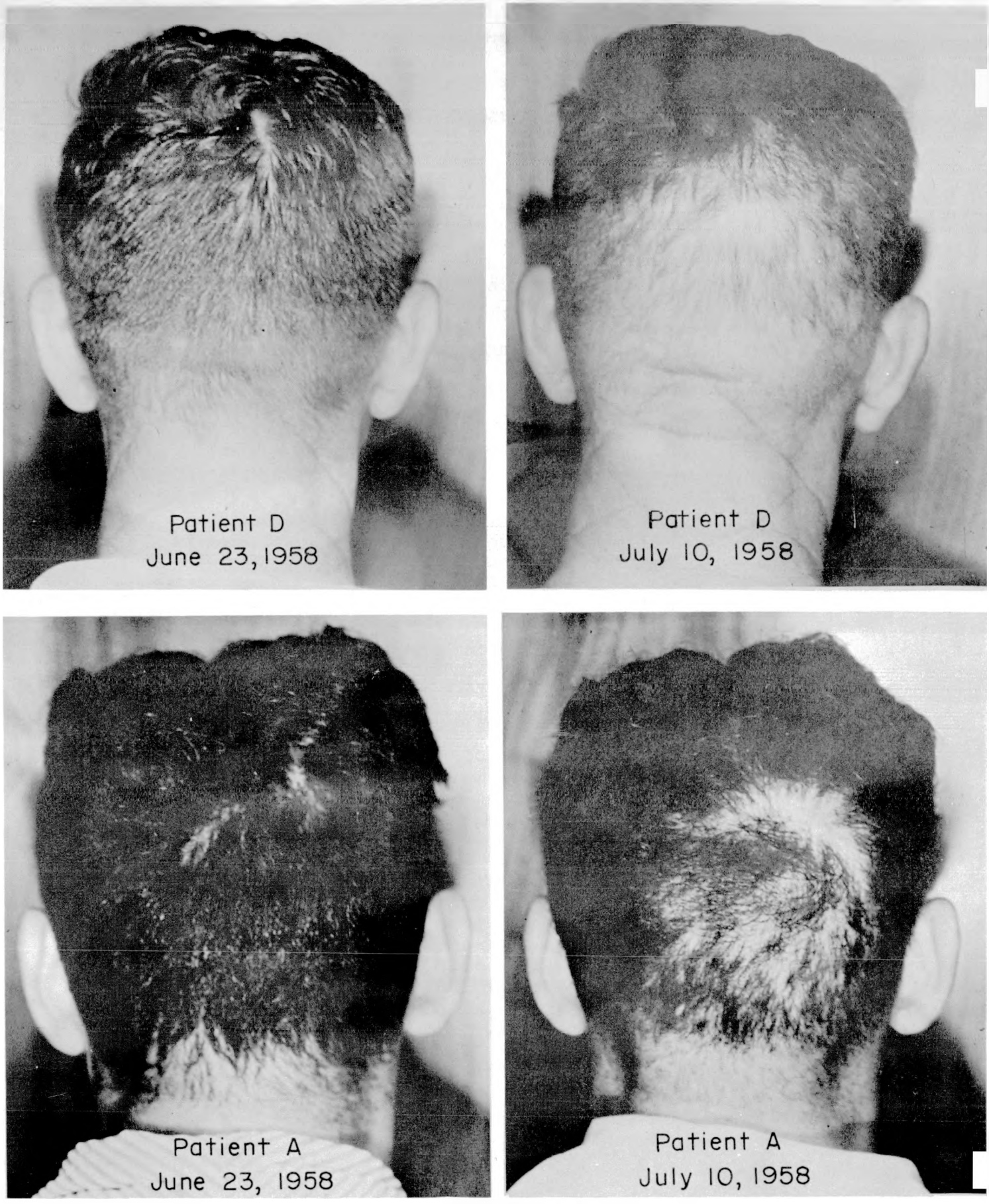

Patient D
June 23, 1958
Patient D
July 10, 1958
Patient A
June 23, 1958
Patient A
July 10, 1958

Figure 2

Infections. Patient E developed a painful small furuncle at the outer margin of the left external auditory canal on the 3rd day. There was no associated elevation in temperature and no specific treatment was instituted. The furuncle drained spontaneously and had completely healed in 10 days. Patient C developed a mild upper respiratory infection with nasal discharge and a slightly productive cough beginning on the 5th hospital day and persisting for about 10 days. Again there was no elevation in temperature and only symptomatic therapy was given. Patient B developed a furuncle in the left gluteal region on the 10th day. This slowly increased in size until it was about 1½ inches in diameter and became fluctuant. Incision and drainage were performed on the 22nd day; healing progressed slowly thereafter and was almost complete at the time of discharge from the hospital. Culture of the exudate showed Staphylococcus epidermidis, plasma coagulase negative. No antibiotics were given in connection with the furuncle. This same patient developed a mild pharyngitis and right otitis media with an elevation in temperature to 38.2° C. on the 13th day. A throat culture was subsequently reported as showing alpha hemolytic streptococci. Therapy with tetracycline was begun and his temperature was normal within 24 hours. The antibiotic was continued for 10 days. Patient A developed a sore throat and elevation in temperature to 38.6° C. on the 31st day. Examination showed yellowish exudate in the tonsillar follicles bilaterally. A culture was subsequently reported as predominately alpha hemolytic streptococci with several colonies of beta hemolytic streptococci. He was given tetracycline therapy and the temperature returned to normal in 48 hours. The antibiotic was continued for 10 days.

Epilation. Loss of hair from the scalps started on the 17th day in all five of the patients in the group first admitted. In Patients A, D, and E soreness of the scalp preceeded the actual loss by two or three days and persisted for several days. Patients A and D developed loss great enough to be obvious on casual observation (see Fig. 2). In these two the greatest loss occurred in the occipital region. No definite correlation could be established between the area of greatest loss and the position of the patient in relation to the source of radiation at the time of the accident. Mechanical rubbing of this portion of the head on the pillow while lying in bed was considered as explaining why the greatest loss occurred in the occipital region. Patient B noted some loss of hair from the chest and Patient E noted loss from the legs. The hair loss had almost stopped in all patients by the time of discharge from the hospital 44 days after exposure but there had been no evidence of beginning regrowth in the two patients in whom this could be judged. (Since release all have completely recovered their hair in about six months.)

Hemorrhagic Tendency. Patient A, who received the largest estimated dose, developed a small patch of petechiae on the abdomen on the 25th day and his gums bled slightly while brushing his teeth on one occasion on this day. At this time his blood platelet count was 2,500 per cu mm. A small ecchymosis appeared spontaneously on the dorsum of

the right foot on the 28th day, when his blood platelet count was 12,500 per cu mm, but there was no further bleeding. Patient C developed a few small petechiae on the legs on the 25th day and during the next four days these became moderately plentiful, scattered over the whole body except the head and neck. His daily blood platelet counts ranged from 12,500 to 22,500 per cu mm during this time. He had no evidence of actual bleeding. Patient E had slight bleeding from the gums on brushing his teeth on the 26th and 27th days but never developed petechiae. His platelet counts were 12,500 and 65,000 per cu mm respectively, on these two days. Patients B and D did not develop petechiae or bleeding. Their blood platelet counts fell to a low of 32,500 and 40,000 per cu mm, respectively.

Hematuria. Patient A had rare red blood cells in the urinary sediment on two consecutive days and Patients B and D, who had neither petechiae or bleeding, showed rare red blood cells in the urinary sediment on one day only. The amount of hematuria seemed hardly significant but it occurred in all three patients from the 25th through the 27th days when blood platelets were most reduced. It was of interest that patients C and E did not show any suggestion of hematuria although Patient C had generalized petechiae and Patient E had slight bleeding from the gums on two occasions.

Melena. Daily stool examinations for occult blood were done on all patients using Hematest® tablets. The patients were not on meat-free diets. Patient B had stool specimens positive for occult blood on the 7th and 8th days and Patient D had the same finding on the 2nd, 16th, 33rd, and 40th days. For Patient D the technician made a notation of "very hard stool" on each occasion. Neither of these men had hemorrhoids or other rectal lesions on routine rectal examination. These were the two patients who showed neither petechiae or gum bleeding. Both of them had rare red blood cells in the urinary sediment on one occasion but not at the time that occult blood was found in the stools. Patients A, C, and E showed no evidence of melena at any time.

Weight. Except for a loss of two pounds by three of the patients during the first few days no weight loss occurred. At the time of discharge all the men showed a gain ranging from three to thirteen pounds.

Weakness. None of the patients complained of pronounced weakness during their hospital care. During the first few days when nausea and vomiting were present there were expressions of mild weakness as part of the over-all ill feeling. During approximately the last two weeks Patients A and C complained of mild weakness and easy fatigability. These two patients experienced the greatest drop in red blood cell values and during this period their hemoglobin determinations ranged from nine to eleven grams, and their hematocrit from 25 to 32 per cent. It was believed that this might account for their symptoms.

Psychological Factors. There were no major psychological disturbances in any of the patients. The possibility of psychological factors playing a role in some of the nausea and vomiting in two of them has already been mentioned. In the latter part of the hospital stay there were occasional, isolated expressions of resentment toward venipunctures and bone-marrow aspirations. In general the patients were a very cooperative group and complied readily with all requests made of them.

The clinical developments are summarized in Table 2.

Case Reports

Patient A

This 40-year-old white, married man, a chemical operator, was standing about six feet from the source of radiation at the time of the accident and received an estimated dose of 365 rads. He had the onset of nausea about two hours after the accident and vomited two or three times in the next two hours. He received an injection of prochlorperazine dimaleate for the nausea and vomiting at the plant dispensary. He noted no other symptoms. After his admission to the hospital, about 11 hours after the accident, nausea persisted without vomiting.

Past History. He had had only the usual childhood diseases with no sequelae.

Systems Review. Occasional mild headaches; occasional "indigestion," nausea, and vomiting that he attributed to dietary indiscretion; increased frequency of urination and occasional nocturia for three or four years; no history of orchitis.

Family History. His wife was 35 years old; they had two children, 16 and 3 years old, living and well. His father had died from cancer of the stomach at 45 years of age. His mother, age 60, was living and had known heart disease; one grandparent had died of heart disease. All siblings were living and well.

Physical Examination. Temperature, 37° C; pulse, 72 per minute; respirations, 18 per minute; blood pressure, 112/64 mm Hg; height, 5 feet, 11½ inches; weight, 172 pounds. The patient was well-developed, and well-nourished, complaining of nausea, but in no acute distress; no evidence of recent trauma; no erythema or other abnormality of the skin except for multiple pigmented nevi scattered over the body; no significant abnormal physical observations.

Table 2
Summary of Clinical Developments

Patient	Estimated Dose (rads)	Gastrointestinal Symptoms	Infections, Fever and Use of Antibiotics	Hair Loss (Started 17th Day)	Weight Change
A	365	Vomiting, 2 days duration; nausea, 5 days duration; no diarrhea	Acute tonsillitis, temp., 38.6° C, 31st day; treated with tetracycline	Soreness of scalp followed by hair loss; mostly in occipital region	-2 lb +8 lb
B	270	Vomiting, 2 days duration; nausea, 3 days duration; no diarrhea	Furuncle, left gluteal region, starting 10th day; incision and drainage 22nd day; no associated fever; pharyngitis and right otitis media, 13th day, temp. 38.2° C; treated with tetracycline	Slight; no soreness of scalp; loss on chest also	-2 lb +13 lb
C	339	Slight nausea, brief duration, 2nd day; no vomiting; no diarrhea	Mild upper respiratory infection, starting 10th day; no fever; no specific treatment	Slight; no soreness of scalp	+8 lb
D	327	Nausea and vomiting, 4 days duration; associated vague discomfort in epigastrium and left chest, 3rd and 4th days; episode RIQ pain, 24th day; no diarrhea	None	Soreness of scalp followed by hair loss; mostly in occipital region	-2 lb +3 lb
E	236	Nausea and vomiting, 2 days duration; no diarrhea	Small furuncle, external auditory canal, 3rd day; no fever; no specific treatment	Slight; soreness of scalp; loss on legs also	+10 lb

Table 2 (continued)

Patient	Estimated Dose (rads)	Petechiae	Bleeding	Hematuria	Melena
A	365	Few petechiae on abdomen on 25th day; small ecchymosis on foot on 28th day	Gums bled on brushing teeth on 25th day	Rare RBC on 25th and 26th days	None
B	270	None	None	Rare RBC on 27th day	Occult blood on 7th and 8th days
C	339	Generalized over trunk and legs starting on 25th day	None	None	None
D	327	None	None	Rare RBC on 25th day	Occult blood on 2nd, 16th, 33rd, and 40th days
E	236	None	Gums bled on brushing teeth on 26th and 27th days	None	None

Laboratory Studies on Admission.
Hemoglobin, 14.8 g
Hematocrit, 41 per cent
White blood cell count, 7,850 per cu mm:
  Band neutrophils, 2 per cent
  Segmented neutrophils, 76 per cent
  Lymphocytes, 16 per cent
  Monocytes, 4 per cent
  Eosinophils, 1 per cent
  Basophils, 1 per cent
Blood platelet count, 162,500 per cu mm
Reticulocytes, 0.7 per cent
Sedimentation rate, 8 mm per hour corrected
Urinalysis:
  Specific gravity, 1.031
  No albuminuria or glycosuria
  Only amorphous sediment on microscopic examination
Blood nonprotein nitrogen, 32 mg per 100 ml
Fasting blood sugar, 92 mg per 100 ml
Total serum proteins, 7 g per 100 ml
  Albumin, 4.9 g per 100 ml
  Globulin, 2.1 g per 100 ml
Serum sodium, 139 mEq per liter
Serum potassium, 4.8 mEq per liter
Serum chloride, 99 mEq per liter
CO_2 combining power, 54 volumes per cent
Serum calcium, 9.0 mg per 100 ml
Serum phosphorus, 3.3 mg per 100 ml
Serum alkaline phosphatase, 1.9 Bessey-Lowry units
Serum uric acid, 5.8 mg per 100 ml
Total blood cholesterol, 174 mg per 100 ml
Cholesterol esters, 137 mg per 100 ml
Serum lactic dehydrogenase, 150 units
Serum glutamic oxaloacetic transaminase, 16 units
Serum glutamic pyruvic transaminase, 10 units
Throat culture:
  Usual throat flora with alpha hemolytic streptococci predominating and a few colonies of beta hemolytic streptococci
Chest X ray:
  Scattered calcific densities in both lung fields; some calcification in the left hilum; no evidence of active pulmonary disease

Hospital Course. During the first 24 hours in the hospital the patient had no further vomiting, ate all three meals, and was essentially asymptomatic. About 1:00 a.m. of the 2nd hospital day, however, he became nauseated and vomited several times during the next 24 hours. He was given two intramuscular injections of 50 mg of promazine hydrochloride during this period. The vomiting subsided and did not recur

during the remainder of his hospital stay, but he continued to complain of some nausea through the first five days. He received perphenazine, 4 mg every six hours orally, for this complaint, beginning on the 2nd day and continuing for seven days. He was then without complaints until the 16th day when he complained of soreness of the scalp. On the 17th day loss of hair from the scalp began and continued throughout the remainder of his hospital stay, ceasing about the time of discharge on the 44th day. Although there was loss from the entire scalp, it was most noticeable over the occipital region, which became almost bare. Except for the epilation, he felt well and showed no abnormal signs or symptoms until the 25th day when a patch of petechiae appeared on the abdomen. His gums bled slightly while he was brushing his teeth on one occasion on the 25th day. At this time his blood-platelet count was at its lowest level of 2,500 per cu mm. Rare red blood cells were seen in the urinary sediment on the 25th and 26th days but none were present on daily urine examinations otherwise. Daily stool examinations for occult blood were all negative. The patient was afebrile throughout his time in the hospital until the 31st day when he developed a sore throat and elevation in temperature to 38.2° C. Examination showed a purulent exudate in the tonsillar follicles. A throat culture was obtained and therapy with tetracycline, 250 mg every four hours orally, was started. The throat culture was subsequently reported as showing the usual throat flora with alpha hemolytic streptococci predominating and several colonies of beta hemolytic streptococci. His temperature returned to normal in 72 hours and his symptoms subsided. The antibiotic was continued for 10 days. During the last two weeks (approximately) in the hospital he complained of weakness and easy fatigability of mild degree. During this time his hemoglobin determination ranged from 9.1 g to 10.7 g and the hematocrit from 25 per cent to 30 per cent, having slowly and progressively fallen to these values from the admission levels. At the time of discharge his blood-platelet count had increased to 477,500 per cu mm from a low of 2,500 per cu mm on the 25th day and his white blood cell count had increased to 3,600 per cu mm from a low of 800 per cu mm on the 29th day. The admission weight of 172 pounds dropped to 170 pounds on the 6th day with a progressive gain thereafter to 180 pounds at the time of discharge. The patient was discharged from the hospital after 44 days to continue convalescence at home and to be followed as an outpatient every two days.

Patient B

This 32-year-old white, married, man, an electrician, was about 15 feet from the source of radiation at the time of the accident and received an estimated dose of 270 rads. He had onset of nausea and vomiting about four hours after the accident and this persisted intermittently until the time of admission to the hospital, about 11 hours after the accident. He received an injection of prochlorperazine dimaleate for this difficulty at the plant dispensary. The only other

symptom noted was a feeling of thickness and dryness of the tongue.

Past History. Surgery for "rectal cysts" in 1944.

Systems Review. Treatment for sinusitis for several years; upper respiratory infection with cough and sore throat during preceding week; no history of orchitis.

Family History. His father had died at age 53 of cancer; his mother and two siblings were living and well; his wife and two children were also living and well.

Physical Examination. Temperature, 36.5° C; pulse, 90 per minute; respirations, 18 per minute; blood pressure, 140/84 mm Hg; height, 6 feet; weight, 217 pounds. The patient was well-developed; moderately obese; moderately severe nausea; a scar with keloid formation superior to the right ear; mild acne over the upper back; no erythema of the skin; no evidence of recent injury; moderate, diffuse redness of throat without exudate. The examination was otherwise not remarkable.

Laboratory Studies on Admission.
Hemoglobin, 16.7 g
Hematocrit, 47 per cent
White blood cell count, 9,400 per cu mm:
  Band neutrophils, 1 per cent
  Segmented neutrophils, 80 per cent
  Lymphocytes, 14 per cent
  Monocytes, 5 per cent
Blood platelet count, 125,000 per cu mm
Reticulocytes, 1.0 per cent
Sedimentation rate, 7 mm per hour corrected
Urinalysis:
  Specific gravity, 1.015
  No albuminuria or glycosuria
  An occasional white blood cell on microscopic examination
Blood nonprotein nitrogen, 38 mg per 100 ml
Fasting blood sugar, 95 mg per 100 ml
Total serum protein, 7.0 g per 100 ml
  Albumin, 5.0 g per 100 ml
  Globulin, 2.0 g per 100 ml
Serum sodium, 137 mEq per liter
Serum potassium, 4.7 mEq per liter
Serum chlorides, 98 mEq per liter
CO_2 combining power, 55 volumes per cent
Serum calcium, 9.5 mg per 100 ml
Serum phosphorus, 3.7 mg per 100 ml
Serum alkaline phosphatase, 2.4 Bessey-Lowry units
Serum uric acid, 5.3 mg per 100 ml
Total blood cholesterol, 233 mg per 100 ml
Cholesterol esters, 128 mg per 100 ml

Serum lactic dehydrogenase, 200 units
Serum glutamic oxaloacetic transaminase, 14 units
Serum glutamic pyruvic transaminase, 4 units
Throat culture:
Usual throat flora with alpha hemolytic streptococci predominating and several colonies of beta hemolytic streptococci.
Chest X ray:
Lung fields, heart, and great vessels within normal limits; mild osteoarthritic changes of the dorsal spine

Hospital Course. The patient remained nauseated after admission to the hospital and vomited twice during the remaining six hours of the night. For the rest of the first 24 hours, however, he felt quite well and ate all three meals without difficulty. During the early morning hours of the 2nd hospital day he again became nauseated and vomited on one occasion. He experienced no further vomiting but mild nausea persisted for a total of three days. On the 10th day he developed a furuncle in the left gluteal region for which daily hot soaks were instituted. On the 13th day he developed a temperature of 38.2° C and headache. Examination showed a mild infection of the pharynx without exudate and signs of early right otitis media. A throat culture was obtained and treatment with tetracycline, 250 mg every six hours orally, was started. The throat culture was subsequently reported as showing the usual throat flora with alpha streptococci predominating. His temperature returned to normal within 24 hours and the symptoms rapidly subsided. The antibiotic was continued for 12 days. On the 17th day he noticed onset of loss of hair from the scalp (the patient was previously bald on top of the head). This was not preceded by soreness of the scalp, proved to be slight, and persisted for about 10 days. He also noted a slight loss of hair from the chest. By the 22nd day the furuncle in the left gluteal region had become soft and fluctuant with a surrounding area of redness about 1½ inches in diameter. Incision and drainage were performed and about 10 cc of bloody, yellow exudate having the appearance of sebaceous material was obtained. Culture of this material was reported as Staphylococcus epidermidis, plasma coagulase negative. This lesion slowly and progressively healed by secondary intention without any exudate formation; this may have been an indication of the supression in white blood cell formation, which the patient was experiencing during this time. The blood platelet count reached its lowest value of 32,500 per cu mm on the 29th day. The patient developed no petechiae and had no active bleeding. Rare red blood cells were seen in the urinary sediment on the 27th day only. No blood was detected in the stools on daily examination during the period of greatest platelet depression; however, tests for occult blood in the stool were positive on the 7th and 8th days. The blood platelet count increased from its lowest value to 180,000 per cu mm on the 42nd day. The white blood cell count reached its lowest value of 1,650 per cu mm on the 33rd day and increased thereafter to 3,250 per cu mm at the time of discharge. The hemoglobin and hematocrit values at the

time of discharge were 13.7 g and 38 per cent respectively; no lower values had been present during the period in the hospital. On the 5th day the patient's weight was two pounds less than on admission; thereafter, he gained and on discharge weighed 13 pounds more than on admission. The patient was discharged on the 44th hospital day to continue convalescence at home and to be followed as an outpatient every two days.

Patient C

This 39-year-old white, married, man, a machinist, was about 17 feet from the source of radiation at the time of the accident and received an estimated dose of 339 rads. He experienced neither nausea nor vomiting after the accident and his only symptoms consisted of a feeling of warmth all over his body and dryness of the mouth. He had received no medication before his admission to the hospital, about 11 hours after the accident.

Past History. He had had mumps in 1940, complicated by bilateral orchitis, but had recovered without known sequelae and his wife had given birth to two children since that time; he had had total dental extractions in 1955 without abnormal bleeding or other difficulties.

Systems Review. Negative except for items mentioned in Past History.

Family History. His father was living at age 65 with a history of duodenal ulcer; his mother, age 60, wife, age 41, four children, ranging in age from 20 to 11 years, and two siblings were all living and well; no familial diseases were known.

Physical Examination. Temperature, 37.1° C; pulse, 72 per minute; respirations, 20 per minute; blood pressure, 114/66 mm Hg; height, 6 feet, 1¼ inches; weight, 134 pounds. The patient was well-developed, well-nourished, and in no distress; no evidence of recent trauma except for a 2 cm minor laceration on the right forearm four or five days old; no erythema of the skin; slight infection of the pharynx; testicles small, soft, and atrophic bilaterally, more pronounced on the left; no other significant abnormal observations.

Laboratory Studies on Admission.
Hemoglobin, 13.3 g
Hematocrit, 40 per cent
White blood cell count, 11,750 per cu mm:
- Segmented neutrophils, 83.5 per cent
- Lymphocytes, 14.5 per cent
- Monocytes, 1.5 per cent
- Basophils, 0.5 per cent

Blood platelet count, 177,500 per cu mm
Reticulocytes, 0.6 per cent
Sedimentation rate, 8 mm per hour corrected
Urinalysis:
  Specific gravity, 1.005
  No abnormal observations
Blood nonprotein nitrogen, 26 mg per 100 ml
Fasting blood sugar, 91 mg per 100 ml
Total serum protein, 6.7 g per 100 ml
  Albumin, 4.7 g per 100 ml
  Globulin, 2.0 g per 100 ml
Serum sodium, 139 mEq per liter
Serum potassium, 5.2 mEq per liter
Serum chlorides, 98.5 mEq per liter
CO_2 combining power, 51 volumes per cent
Serum calcium, 9.1 mg per 100 ml
Serum phosphorus, 3.5 mg per 100 ml
Serum alkaline phosphatase, 2.1 Bessey-Lowry units
Serum uric acid, 5.4 mg per 100 ml
Total blood cholesterol, 210 mg per 100 ml
Cholesterol esters, 131 mg per 100 ml
Serum lactic dehydrogenase, 240 units
Serum glutamic oxaloacetic transaminase, 10 units
Serum glutamic pyruvic transaminase, 2 units
Throat culture:
  Usual throat flora with alpha hemolytic streptococci predominating.
Chest X ray:
  Increased translucency of the lungs with an increase in AP diameter of the chest suggestive of pulmonary emphysema and minimal fibrosis with a small bleb in the right apex

Hospital Course. The patient was essentially asymptomatic during the first 30 hours in the hospital. On awakening the morning of the 2nd hospital day, when three of his companions in the ward were experiencing nausea and vomiting, he became nauseated but this subsided in about 30 minutes without vomiting. The patient was asymptomatic thereafter until the 10th day when he developed an upper respiratory infection with a slightly productive cough but without elevation in temperature. He received symptomatic treatment only and the infection subsided without complications in about 10 days. On the 17th day he had an onset of loss of hair from the scalp. This was not preceded by soreness of the scalp as was true with some of the other patients. The hair loss was only slight and persisted about two weeks. On the 25th day he developed itching over the legs and examination showed elevation and erythema of the hair follicles, with a few small petechiae on the legs. Over the next 5 days he developed generalized, small, pin-point petechiae over the legs, trunk, and shoulders. His blood platelet count reached its lowest level of 12,500 per cu mm on the 28th day. There was no evidence of active bleeding and daily

examinations of the urine and stools for blood were negative. The petechiae gradually faded and the patient was asymptomatic throughout the remainder of his hospital stay except for mild weakness and fatigue. There had been a slowly progressive drop in hemoglobin and hematocrit values from admission to levels of 10.5 g and 32 per cent, respectively, at the time of discharge and it was thought this might account for these symptoms. At the time of discharge his blood platelets had increased to 180,000 per cu mm. His white blood cell count reached its lowest point of 950 per cu mm on the 30th day and gradually increased thereafter to 5,500 per cu mm on the day of discharge. He experienced no weight loss and on discharge showed a gain of eight pounds over his admission weight. The patient was discharged on the 44th hospital day to continue convalescence at home and to be followed every two days as an outpatient.

Patient D

This 51-year-old white, married, man, an electrician, was about 16 feet from the source of radiation at the time of the accident and received an estimated dose of 327 rads. About two hours after the accident he had the onset of headache, nausea, and vomiting and vomited about 12 times during the next two hours. He received an injection of prochlorperazine dimaleate for these symptoms at the plant dispensary. His symptoms had almost completely subsided by the time of admission to the hospital about 11 hours after the accident.

Past History. He had had mumps about 20 years previously and, although there was no known complication, he and his wife had had no children since that time; he assumed that this was a result of the mumps. Sustained bruises of the left side of his face had been acquired in an automobile accident nine years previously.

Systems Review. Essentially negative.

Family History. His wife and one child, age 23 years, were living and well. No familial diseases were known.

Physical Examination. Temperature, 36.6° C; pulse, 64 per minute; respirations, 18 per minute; blood pressure, 112/74 mm Hg; height, 5 feet, 9 3/4 inches; weight, 169½ pounds. The patient was well-developed and well-nourished, in no acute distress; no evidence of recent trauma; mild erythema from sunburn over face and upper back (confirmed by patient); no other significant physical observations.

Laboratory Studies on Admission.
Hemoglobin, 15.4 g
Hematocrit, 44 per cent
White blood cell count, 6,600 per cu mm:

Band neutrophils, 2 per cent
Segmented neutrophils, 60 per cent
Lymphocytes, 30 per cent
Monocytes, 3.5 per cent
Basophils, 0.5 per cent
Blood platelet count, 230,000 per cu mm
Reticulocytes, 1.5 per cent
Sedimentation rate, 8 mm per hour corrected
Urinalysis:
Specific gravity, 1.030
No albuminuria or glycosuria
An occasional white blood cell and a large amount of mucous shreds on microscopic examination
Blood nonprotein nitrogen, 39 mg per 100 ml
Fasting blood sugar, 94 mg per 100 ml
Total serum protein, 6.9 g per 100 ml
Albumin, 4.7 g per 100 ml
Globulin, 2.2 g per 100 ml
Serum sodium, 136 mEq per liter
Serum potassium, 4.8 mEq per liter
Serum chlorides, 96 mEq per liter
CO_2 combining power, 55 volumes per cent
Serum calcium, 9.1 mg per 100 ml
Serum phosphorus, 3.8 mg per 100 ml
Serum alkaline phosphatase, 2.2 Bessey-Lowry units
Serum uric acid, 7.5 mg per 100 ml
Total blood cholesterol, 252 mg per 100 ml
Cholesterol esters, 124 mg per 100 ml
Serum lactic dehydrogenase, 250 units
Serum glutamic oxaloacetic transaminase, 17 units
Serum glutamic pyruvic transaminase, 3 units
Throat culture:
Usual throat flora with Neisseria flavus predominating
A few colonies of beta hemolytic streptococci and pneumococci
Chest X ray:
Lung fields clear; minimal tortuosity of the aorta; mild changes of hypertrophic arthritis of the dorsal spine

Hospital Course. The patient continued to have some nausea during the first few hours in the hospital. This subsided and he ate all three meals on the first day without difficulty. On awakening the 2nd morning, when three of his companions in the ward were having nausea and vomiting, he again became nauseated and vomited one time. Later in the day he complained of some vague discomfort, without definitive characteristics, in the region of the left scapula. On the 3rd day this discomfort was described as a "pulling sensation" extending from the mid-epigastrium through the left chest to the region of the left scapula. Examination of the heart, chest, and abdomen revealed no abnormality. That evening he again developed nausea, did not eat the evening meal, vomited on one occasion and was given 50 mg promazine hydrochloride

intramuscularly. He remained nauseated and vomited on one occasion on the 4th hospital day but by midday these symptoms subsided and did not recur. The vague discomfort persisted for several days. Repeated physical examinations showed no abnormalities; an electrocardiogram was within normal limits; there was no increase in the sedimentation rate and no elevation of temperature. This discomfort was never severe enough to confine the patient to bed and no definite explanation for it was found. On the 17th day he noticed onset of loss of hair from the scalp preceded by soreness of the scalp. The hair loss progressed quite rapidly and by the 19th day there was a moth-eaten appearance over the occipital region where the hair loss was most pronounced. The hair loss continued throughout the remainder of his hospital stay with the occipital region becoming quite bare. There was no evidence of regrowth by the time of discharge. On the 24th day, although he did not complain voluntarily, it was noticed that he remained in bed most of the day and on direct questioning he reported moderately severe pain in the right lower quadrant, without other associated symptoms. Repeated examinations showed only slight tenderness in the right lower quadrant. He was given antispasmotics and sedatives and observed. By the following morning the pain had almost completely subsided and he did not again complain of it spontaneously. Nevertheless, throughout the remainder of his hospitalization, when questioned directly, he reported that he had continuing intermittent vague discomfort. At the time of this episode his daughter reported that he had experienced episodes of abdominal discomfort intermittently for several years although the patient had not given this history either on admission or at the time of the episode. This had never been severe enough to cause him to seek medical attention. His blood platelet count reached its lowest point of 40,000 per cu mm on the 24th day and increased thereafter to 252,500 per cu mm on the 43rd day. He developed no petechiae or evidence of active bleeding. Rare red blood cells were seen in the urinary sediment on the 25th day only. No blood was detected in the stools during the period of greatest platelet depression; however, daily tests for occult blood were positive on the 2nd, 16th, 25th, 33rd, and 40th days. On each of these occasions the notation was made of "very hard specimen." The lowest white blood cell count was obtained on the 36th day when it was 2,050 per cu mm. It increased thereafter to 3,750 per cu mm before discharge. The lowest values for hemoglobin and hematocrit were 13 g and 37 per cent, respectively, on the 19th day with only slight fluctuations thereafter. The patient was afebrile throughout the hospitalization. A maximum drop in weight of two pounds occurred on the 4th day and on discharge he had gained 3 pounds over the admission weight. The patient was discharged on the 44th day to continue convalescence at home and be followed as an outpatient every two days.

Patient E

This 35-year-old, white, married, man, a machinist, was about 22 feet from the source of radiation at the time of the accident and received an estimated dose of 236 rads. A few hours after the accident he developed nausea but no vomiting and received an injection at the plant dispensary for this symptom. No other symptoms were noted and on admission to the hospital about 11 hours after the accident he was asymptomatic.

Past History. He had had the usual childhood diseases without sequelae; a shotgun injury in the right ankle in military service in 1944 required surgical treatment; hemorrhoidectomy, 1954; no history of orchitis.

Family History. His wife and four children were living and well; no familial diseases were known.

Systems Review. Essentially negative.

Physical Examination. Temperature, 36.2° C; pulse, 56 per minute minute; respirations, 18 per minute; blood pressure, 110/70 mm Hg; height, 6 feet, ½ inch; weight, 164½ pounds. The patient was well-developed, well-nourished, in no distress. Erythema of the skin from a recent sunburn (confirmed by the patient) over upper back, face, and shoulders; lipoma below right clavicle; no other skin lesions; no evidence of recent trauma; small, firm, nontender, freely movable lymph nodes present in axillary and inguinal regions bilaterally; left testicle soft and atrophic; surgical scar over anterior aspect of right ankle with some limitation of motion in this joint; no other significant abnormal physical observations.

Laboratory Studies on Admission.
Hemoglobin, 16.2 g
Hematocrit, 45 per cent
White blood cell count, 5,250 per cu mm:
  Band neutrophils, 2 per cent
  Segmented neutrophils, 71 per cent
  Lymphocytes, 20 per cent
  Monocytes, 4 per cent
  Eosinophils, 3 per cent
Blood platelet count, 145,000 per cu mm
Reticulocytes, 0.3 per cent
Sedimentation rate, 3 mm per hour uncorrected
Urinalysis:
  Specific gravity, 1.032
  No albuminuria or glycosuria
  An occasional white blood cell on microscopic examination
Blood nonprotein nitrogen, 36 mg per 100 ml
Fasting blood sugar, 84 mg per 100 ml

Total serum protein, 6.6 g per 100 ml
  Albumin, 4.7 g per 100 ml
  Globulin, 1.9 g per 100 ml
Serum sodium, 137 mEq per liter
Serum chlorides, 99 mEq per liter
Serum potassium, 5.2 mEq per liter
CO_2 combining power, 50 volumes per cent
Serum calcium, 9.0 mg per 100 ml
Serum phosphorus, 3.2 mg per 100 ml
Serum alkaline phosphatase, 2.0 Bessey-Lowry units
Serum uric acid, 5.3 mg per 100 ml
Total blood cholesterol, 190 mg per 100 ml
Cholesterol esters, 146 mg per 100 ml
Serum lactic dehydrogenase, 290 units
Serum glutamic oxaloacetic transaminase, 7 units
Serum glutamic pyruvic transaminase, 1 unit
Throat culture:
  Usual throat flora with beta hemolytic streptococci predominating
Chest X ray:
  A calcific density in the left apex and another one in the left hilum without other abnormalities

Hospital Course. During the first 24 hours in the hospital the patient was asymptomatic, ate all three meals, and felt well. During the early morning hours of the 2nd day he developed nausea and vomited on three occasions. He received two intramuscular injections of 25 mg of chlorpromazine hydrochloride during the day. Rather severe nausea persisted throughout the day and then subsided with no recurrence while he was in the hospital. On the 3rd day a small painful furuncle appeared on the outer margin of the left external auditory canal. There was no associated elevation of temperature; this lesion drained spontaneously and healed during the next 10 days without specific therapy. The patient had no complaints subsequently until the 16th day when he complained of soreness of the scalp. Loss of hair from the scalp began on the 17th day and persisted for about two weeks. The hair loss was slight and not obvious on casual observation. On the 26th day he noticed increased loss of hair from the legs; this loss persisted for several days. His blood platelet count reached its lowest level of 12,500 per cu mm on the 26th day. There was slight bleeding from the gums on brushing the teeth on the 26th and 27th days. The patient did not develop petechiae and no blood was detected in the urine or stools on daily examinations. He was asymptomatic throughout the remainder of his hospital stay and afebrile throughout his entire hospital course. The hemoglobin and hematocrit reached their lowest values of 13.5 g and 39 per cent, respectively, on the 43rd day. The blood platelets increased from the lowest count of 12,500 per cu mm on the 26th day to 147,500 per cu mm at the time of discharge. The white blood cell count reached its lowest point of 2,300 per cu mm on the 33rd day and had increased to 4,700 per cu mm at discharge. There was no weight loss and a gain

of 10 pounds during the hospital stay. The patient was discharged on the 44th hospital day to continue convalescence at home and to be followed as an outpatient every two days.

Patient F

This 41-year-old, white, married, man, a welder, was on a mezzanine floor approximately above Patient E at the time of the accident and received an estimated dose of 68.5 rads. He was admitted to the hospital on June 18, 1958, for observation. He reported that he had experienced no unusual symptoms and had felt well since the accident.

Past History. He had been admitted to a hospital in 1929 for a ruptured appendix and again several years before admission here for a bullet wound through the right upper leg.

Systems Review. He had had a fungus infection of the right foot for the past few years and symptoms of excessive gas and abdominal pain of two years' duration, for which he had never sought medical attention.

Family History. His father died at age 50 of pneumonia complicating a cholecystectomy; his mother and two siblings were living and well; his wife and four children were living and well; no familial diseases were known.

Physical Examination. Temperature, 37.3° C; pulse, 100 per minute; respirations, 21 per minute; blood pressure, 145/85 mm Hg; height, 5 feet, 11 3/4 inches; weight, 200 pounds. The patient was well-developed and well-nourished, slightly obese, in no distress; no evidence of recent trauma; no erythema of the skin, small scars on the right cheek and in left scapular region; scar of alleged bullet wound on medial aspect of right thigh; right foot purple colored from medication for treatment of fungus infection; slight limp involving the right leg on walking; no other significant abnormal physical observations.

Laboratory Studies on Admission.
Hemoglobin, 15.3 g
Hematocrit, 46 per cent
White blood cell count, 10,400:
- Band neutrophils, 1 per cent
- Segmented neutrophils, 67 per cent
- Lymphocytes, 24.5 per cent
- Monocytes, 3 per cent
- Eosinophils, 3.5 per cent
- Basophils, 1 per cent

Blood platelet count, 152,500 per cu mm
Reticulocytes, 1.3 per cent

Sedimentation rate, 3 mm per hour corrected
Urinalysis:
  Specific gravity, 1.011
  No albuminuria or glycosuria
  A rare white blood cell on microscopic examination
Blood nonprotein nitrogen, 27 mg per 100 ml
Fasting blood sugar, 88 mg per 100 ml
Total serum protein, 6.7 g per 100 ml
  Albumin, 4.9 g per 100 ml
  Globulin, 1.8 g per 100 ml
Serum sodium, 138 mEq per liter
Serum potassium, 5.5 mEq per liter
Serum chloride, 99 mEq per liter
CO_2 combining power, 53 volumes per cent
Serum calcium, 9.5 mg per 100 ml
Serum phosphorus, 2.8 mg per 100 ml
Serum alkaline phosphatase, 2.7 Bessey-Lowry units
Serum uric acid, 4.7 mg per 100 ml
Total blood cholesterol, 169 mg per 100 ml
Cholesterol esters, 106 mg per 100 ml
Serum lactic dehydrogenase, 200 units
Serum glutamic oxaloacetic transaminase, 12 units
Serum glutamic pyruvic transaminase, 10 units
Throat culture:
  Usual throat flora with beta hemolytic streptococci predominating
Chest X ray:
  An area of calcification measuring 6 by 5 cm in the left lower lobe, thought to represent calcification in the pleura; evidence of pleural thickening in the left costophrenic sinus; an old healed fracture of the posterior portion of the 8th rib on the right; no evidence of active disease

Hospital Course. The patient was afebrile and asymptomatic throughout his hospital stay. Daily blood counts showed no significant changes in the values for hemoglobin, hematocrit, white blood cells, and platelets. The patient gained five pounds while he was in the hospital. He was discharged on the 9th hospital day to be followed as an outpatient every two days.

Patient G

This 55-year-old, white, married, man, a maintenance mechanic, was on a mezzanine floor above and about six feet beyond Patient F at the time of the accident and received an estimated dose of 68.5 rads. He was admitted to the hospital on June 18, 1958, for observation. During the interval between the accident and admission to the hospital

he had experienced no unusual symptoms and had felt well.

Past History. He had had the usual childhood diseases, and typhoid fever in his youth. One year previously he had had an episode of precordial pain diagnosed as coronary artery disease at which time he was off work for three weeks.

Systems Review. He had a chronic cough and postnasal discharge, worse in the mornings; dyspnea and cardiac palpitations on moderate exertion; nocturia of moderate degree; moderate constipation and external hemorrhoids of five years' duration.

Family History. His father had died of cerebral vascular accident; his mother, wife, and five children were living and well; three children were dead, one from cardiac disease, and two from accidental causes.

Physical Examination. Temperature, 37° C; pulse, 96 per minute; respirations, 20 per minute; blood pressure, 120/80 mm Hg; height, 5 feet, 11 3/4 inches; weight, 166½ pounds. The patient was well-developed and well-nourished, in no distress; no evidence of recent trauma; no erythema or lesions of the skin. Positive physical observations were caries of the teeth, deviated nasal septum, small external hemorrhoids, and moderate enlargement of the prostate gland.

Laboratory Studies on Admission.
Hemoglobin, 15.2 g
Hematocrit, 43 per cent
White blood cell count, 11,700 per cu mm:
  Band neutrophils, 2.5 per cent
  Segmented neutrophils, 73.5 per cent
  Lymphocytes, 17 per cent
  Monocytes, 5.5 per cent
  Eosinophils, 1 per cent
  Basophils, 0.5 per cent
Blood platelet count, 160,000 per cu mm
Reticulocytes, 0.9 per cent
Sedimentation rate, 4 mm per hour corrected
Urinalysis:
  Specific gravity, 1.010
  No albuminuria or glycosuria
  An occasional white blood cell on microscopic examination
Blood nonprotein nitrogen, 32 mg per 100 ml
Fasting blood sugar, 88 mg per 100 ml
Total serum protein, 6.5 g per 100 ml
  Albumin, 4.6 g per 100 ml
  Globulin, 1.9 g per 100 ml
Serum sodium, 143 mEq per liter
Serum potassium, 5.1 mEq per liter
Serum chlorides, 99 mEq per liter

CO_2 combining power, 64 volumes per cent
Serum calcium, 9.0 mg per 100 ml
Serum phosphorus, 3.6 mg per 100 ml
Serum alkaline phosphatase, 2.5 Bessey-Lowry units
Serum uric acid, 4.3 mg per 100 ml
Total blood cholesterol, 179 mg per 100 ml
Cholesterol esters, 112 mg per 100 ml
Serum lactic dehydrogenase, 143 units
Serum glutamic oxaloacetic transaminase, 15 units
Serum glutamic pyruvic transaminase, 6 units
Throat culture:
Usual throat flora with a few colonies of beta hemolytic streptococci
Chest X ray:
A mild degree of pulmonary emphysema and calcific densities in the left lung field and left hilum

Hospital Course. The patient remained afebrile and asymptomatic throughout his hospital stay. There were no significant deviations in clinical or laboratory observations from those present on admission. His weight remained constant. He was discharged on the 10th hospital day to be followed as an outpatient every two days.

Patient H

This 25-year-old, white, single, man, a chemical operator, was about 50 feet from the source of radiation at the time of the accident and received an estimated dose of 22.8 rads. He was admitted to the hospital on June 18, 1958, for observation. About two hours after the accident he developed symptoms of stiff neck, weakness, and nausea, but no vomiting. These symptoms persisted intermittently until the morning of admission.

Past History. He had had the usual childhood diseases; tonsillectomy at age 10; fracture of right clavicle at age 10; surgery for varicose veins of the right leg at age 18.

Systems Review. Negative except for varicose veins involving the left leg.

Family History. His father, age 59, was living and well; mother, age 53, had chronic mental illness; one sister was living and well.

Physical Examination. Temperature, 36.4° C; pulse, 86 per minute; respirations, 18 per minute; blood pressure, 98/62 mm Hg; height, 5 feet, 6½ inches; weight, 140½ pounds. The patient was well-developed and well-nourished, young, in no distress; no evidence of recent trauma; no erythema or lesions of skin. The only positive physical observation was varicose veins involving the left leg.

Laboratory Studies on Admission.
Hemoglobin, 16.5 g
Hematocrit, 47 per cent
White blood cell count, 5,800 per cu mm:
  Band neutrophils, 1 per cent
  Segmented neutrophils, 57 per cent
  Lymphocytes, 33 per cent
  Monocytes, 6 per cent
  Eosinophils, 3 per cent
Blood platelet count, 170,000 per cu mm
Reticulocytes, 0.7 per cent
Sedimentation rate, 1 mm per hour corrected
Urinalysis:
  Specific gravity, 1.010 with no abnormal observations
Blood nonprotein nitrogen, 28 mg per 100 ml
Fasting blood sugar, 88 mg per 100 ml
Total serum protein, 6.7 g per 100 ml
  Albumin, 4.9 g per 100 ml
  Globulin, 1.6 g per 100 ml
Serum sodium, 146 mEq per liter
Serum potassium, 5.4 mEq per liter
Serum chlorides, 103 mEq per liter
CO_2 combining power, 58 volumes per cent
Serum calcium, 9.2 mg per 100 ml
Serum phosphorus, 3.95 mg per 100 ml
Serum alkaline phosphatase, 2.0 Bessey-Lowry units
Serum uric acid, 4.7 mg per 100 ml
Total blood cholesterol, 106 mg per 100 ml
Cholesterol esters, 84 mg per 100 ml
Serum lactic dehydrogenase, 150 units
Serum glutamic oxaloacetic transaminase, 9 units
Serum glutamic pyruvic transaminase, 8 units
Throat culture:
  Usual throat flora
Chest X ray:
  Calcific densities scattered in both lung fields and in both hilar regions; no evidence of active disease

Hospital Course. During the nine days in the hospital the patient was afebrile. His only symptoms were those of an upper respiratory infection, which developed on the 6th day and for which he was given symptomatic therapy. Daily blood counts showed no significant changes in values for hemoglobin, hematocrit, white blood cells, and platelets. He gained four pounds during his stay in the hospital. He was discharged on the 9th hospital day to be followed as an outpatient every two days.

APPENDIX

List of Persons Attending the
Meeting on June 17 at 8:00 p.m.

1. Samuel R. Sapirie, Manager of Operations, ORO
2. Clark E. Center, Vice-President, Union Carbide Nuclear Co.
3. John P. Murray, UCNC, Y-12
4. C. R. Sullivan, M.D., Y-12
5. Charles Keller, ORO
6. Harold J. McAlduff, ORO
7. Dixon Callihan, ORNL, X-10
8. Mario Perez-Reyes, M.D., ORINS
9. Kandiah Shivanandan, ORINS
10. Aikra Tsuya, M.D., ORINS
11. Joseph A. Lenhard, ORO
12. Joseph S. Lyon, M.D., UCNC, K-25
13. Thomas A. Lincoln, M.D., ORNL, X-10
14. C. S. Shoup, ORO
15. Charles C. Congdon, M.D., ORNL, Y-12
16. Karl Z. Morgan, ORNL, X-10
17. John A. Swartout, ORNL, X-10
18. Robert A. Charpie, ORNL, X-10
19. Alexander Hollaender, ORNL, Y-12
20. B. W. Sitterson, M.D., ORINS
21. Howard Harmon, ORINS
22. F. S. Patton, ORNL, X-10
23. K. S. Lane, M.D., UCNC, Y-12
24. Floyd Culler, ORNL, X-10
25. George Harrell, M.D., Univ. of Florida
26. Marshall Brucer, M.D., ORINS
27. Charles L. Dunham, M.D., AEC Hdq.
28. Louis Hempelmann, Univ. of Rochester
29. Eugene Cronkite, M.D., Brookhaven
30. Arthur Rupp, ORNL, X-10
31. Logan Emlet, UCNC, K-25
32. Arthur L. Kretchmar, M.D., ORINS
33. Betty Cooper, M.D., ORINS
34. E. B. Andrews, M.D., ORINS
35. A. C. Morris, Jr., ORINS
36. William Gibbs, ORINS
37. Joe Gray, ORINS
38. William G. Pollard, ORINS
39. Bill M. Nelson, M.D., ORINS
40. G. A. Andrews, M.D., ORINS

HEMATOLOGIC EFFECTS OF THE ACCIDENTAL RADIATION EXPOSURE AT Y-12

G. A. Andrews and B. W. Sitterson
With the technical help of Martha Clevenger and Barbara Unger

Introduction

The accidental radiation exposure that occurred at the Y-12 plant on June 16, 1958, offered an unusual opportunity for detailed hematologic studies of patients exposed to total-body irradiation. Eight persons received significant doses, five in the neighborhood of 300 rads and three between 20 and 70 rads. In these patients the changes following radiation were not complicated by any trauma or superimposed high-level skin radiation, such as have been seen in certain other accidental exposures. There was no alteration in the clinical and laboratory findings that could be attributed to treatment. Another feature of the situation, which adds to the value of the observations, is that it was possible to determine the radiation dose with considerable accuracy.

The present report is a preliminary one on the hematologic changes that occurred in the first 60 days after exposure. It is anticipated that a more complete report will be made subsequently, with inclusion of more follow-up data plus a more detailed study of certain morphologic features of the blood and bone marrow.

Methods

The hematologic studies reported here were all done in the same laboratory except for routine blood counts performed before exposure and during the first two hours after the accident; these were done in the Y-12 dispensary laboratory.

The postirradiation studies were done with standard methods in the hematology laboratory of the ORINS Medical Division. Platelets were counted by the method of Brecher and Cronkite, with an oxalate diluent and the phase microscope. Cover-slip films were stained with Wright's stain. Reticulocyte counts were done on cover slips previously coated

with cresyl blue stain and subsequently stained with Wright's stain. Differential counts were done on 200 or more cells in almost all instances.

The persons exposed are identified by letters as in the previous reports, and dosages estimated are as follows:

A - 365 rads
B - 270 rads
C - 339 rads
D - 327 rads
E - 236 rads

Those with the low levels of radiation were:

F - 68.5 rads
G - 68.5 rads
H - 22.8 rads

Hematologic Values for the Five Men with High Radiation Dose

These five men had all had previous blood counts done at the time of pre-employment and routine yearly physical examinations. Each man had had at least four such blood studies and one had had eight. In none were there any significant abnormal findings. Differentials, done on 100 cells, were generally not remarkable, although there were in general very few monocytes reported and in some patients a mild relative lymphocytosis was sometimes recorded. The pretreatment differential counts may not be entirely comparable to those done in a different laboratory after exposure. Table 1 shows average pre-exposure blood values.

A blood count was done at the dispensary laboratory between 1½ and 2 hours after the accident. Table 2 shows the values obtained. The differential counts were done at the ORINS laboratory on films prepared at the Y-12 dispensary laboratory.

The important postirradiation hematologic values for the five high-dose men are given in Figs. 1 through 7. The values charted do not include the pre-exposure base-line levels. The charts start with the first blood count done at the ORINS Medical Division about 12 hours after the accident, except that the value for the lymphocytes obtained 1½ to 2 hours after exposure is included. Figure 1 is a composite, based upon averages on all five men. In the other figures each patient is represented separately. The same code is used throughout. The day of the radiation exposure is considered the zero day, and the following day is No. 1.

Leukocytes. It is of interest that shortly after exposure all of the men had higher leukocyte counts than their normal pre-exposure

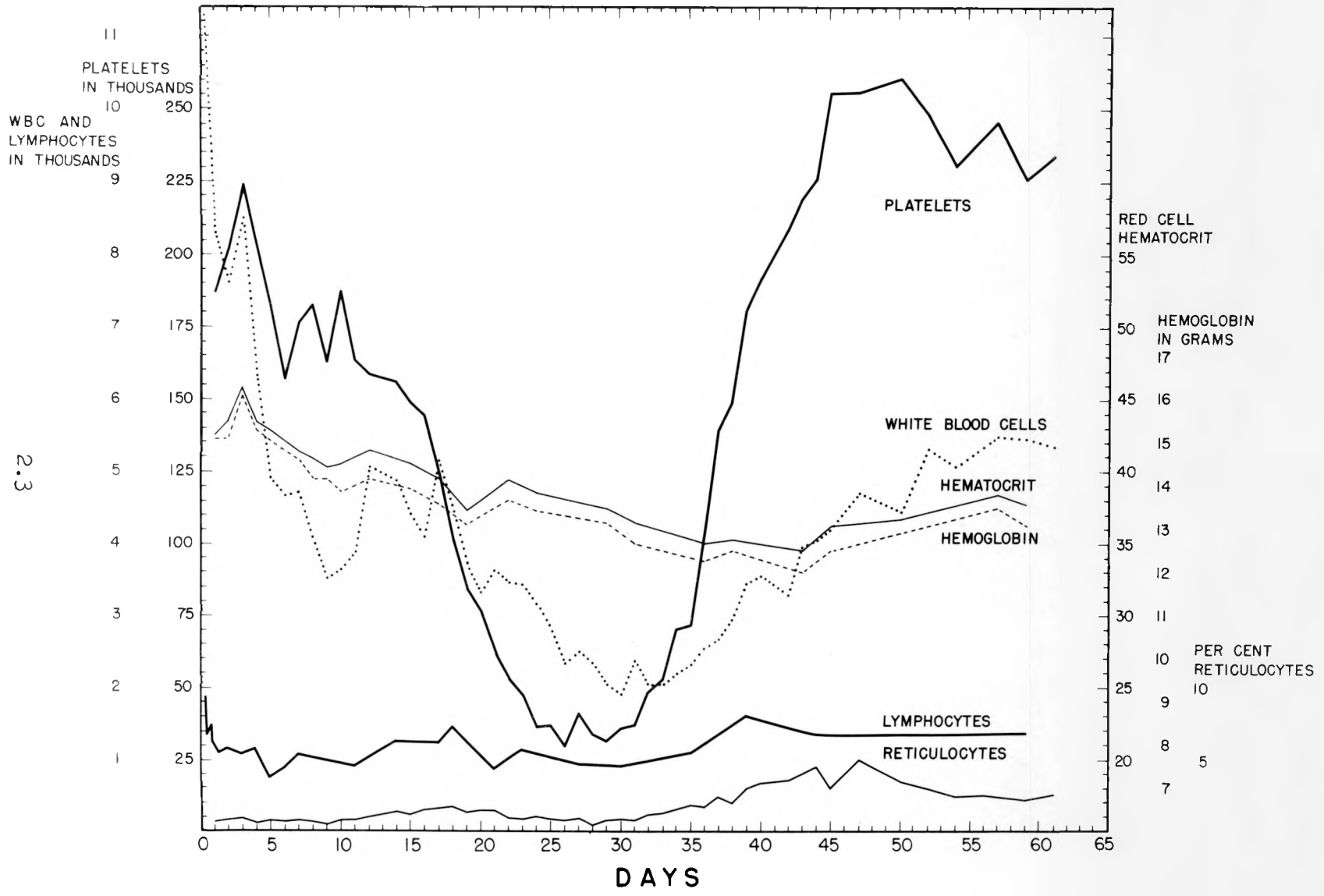

PLATELETS
IN THOUSANDS
WBC AND
LYMPHOCYTES
IN THOUSANDS
PLATELETS
WHITE BLOOD CELLS
HEMATOCRIT
HEMOGLOBIN
LYMPHOCYTES
RETICULOCYTES
RED CELL
HEMATOCRIT
HEMOGLOBIN
IN GRAMS
PER CENT
RETICULOCYTES
DAYS
0 5 10 15 20 25 30 35 40 45 50 55 60 65
11 10 9 8 7 6 5 4 3 2 1
250 225 200 175 150 125 100 75 50 25
55 50 45 40 35 30 25 20
17 16 15 14 13 12 11 10 9 8 7
10 9 8 7 6 5

Figure 1

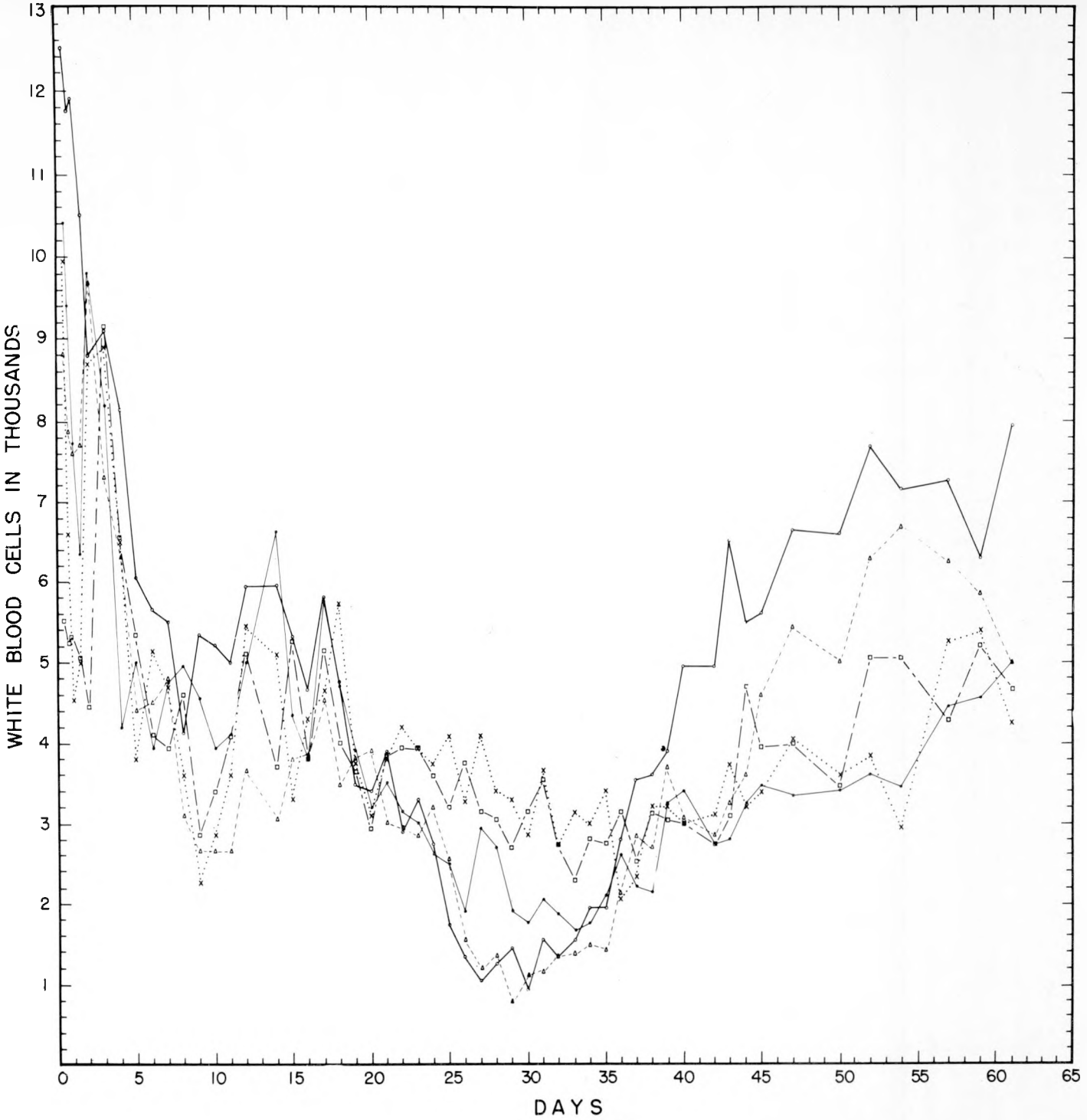

WHITE BLOOD CELLS IN THOUSANDS
13
12
11
10
9
8
7
6
5
4
3
2
1
0
5
10
15
20
25
30
35
40
45
50
55
60
65
DAYS

Figure 2

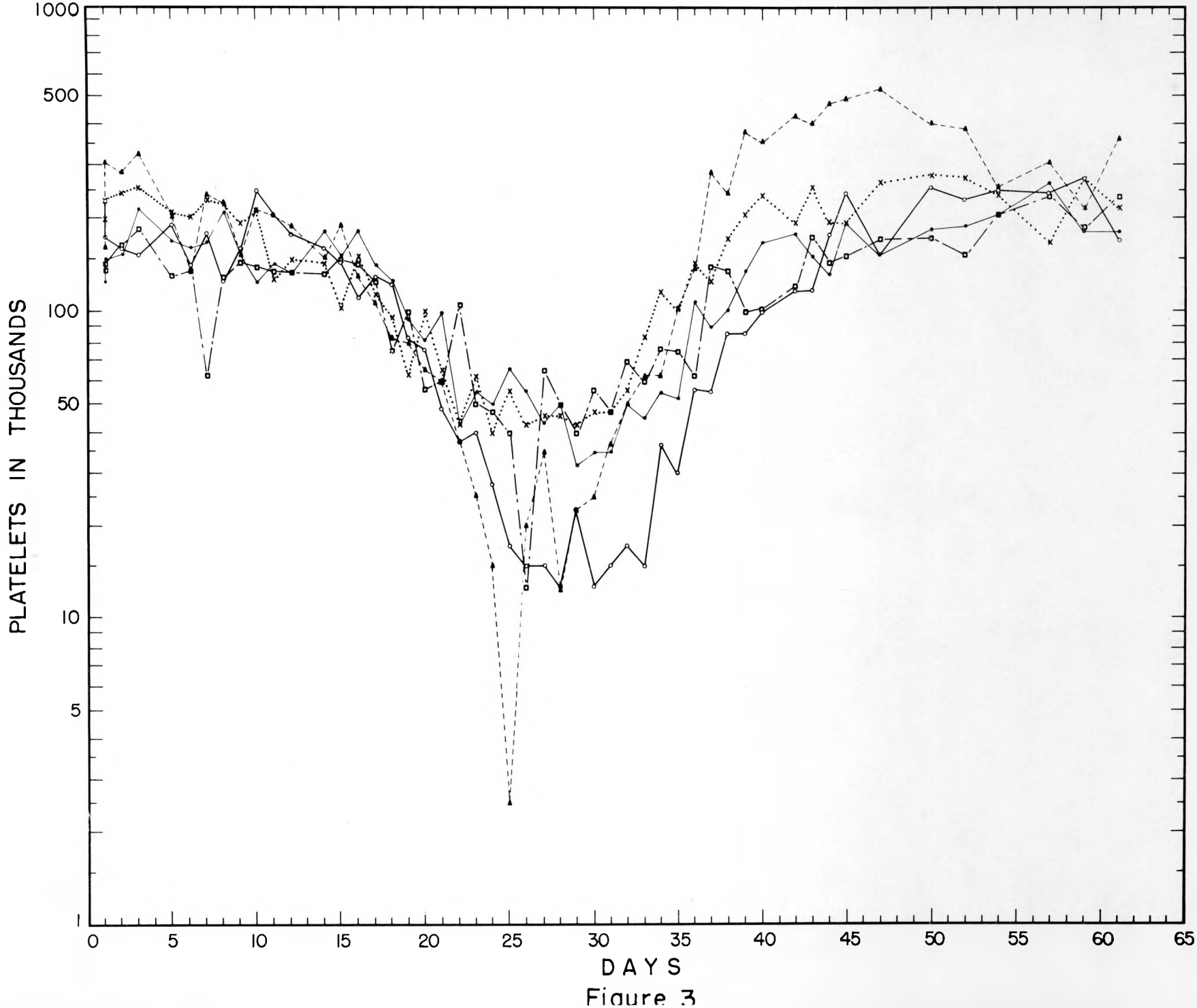

PLATELETS IN THOUSANDS
1000
500
100
50
10
5
1
0
5
10
15
20
25
30
35
40
45
50
55
60
65
DAYS

Figure 3

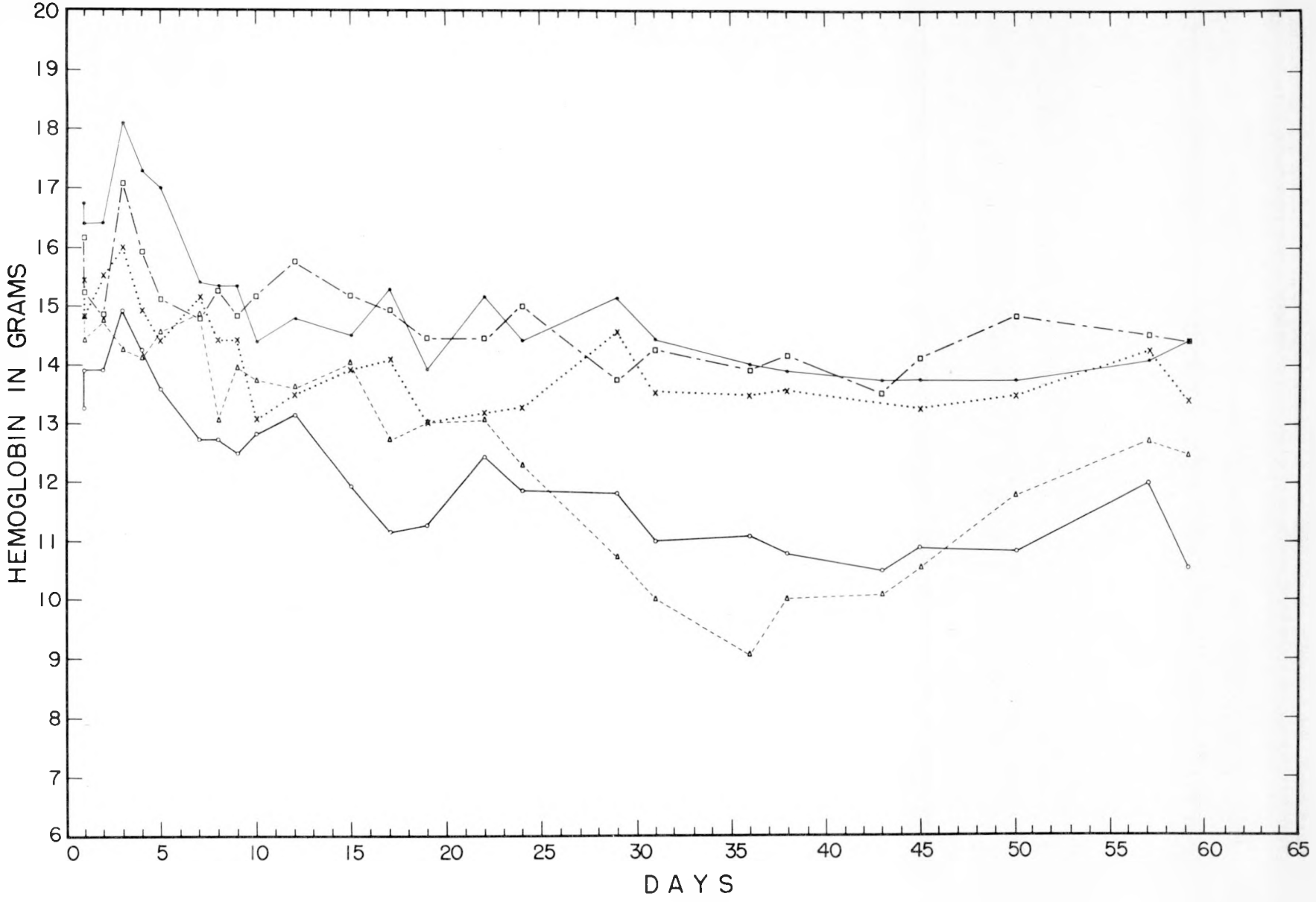

HEMOGLOBIN IN GRAMS
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
0
5
10
15
20
25
30
35
40
45
50
55
60
65
DAYS

Figure 4

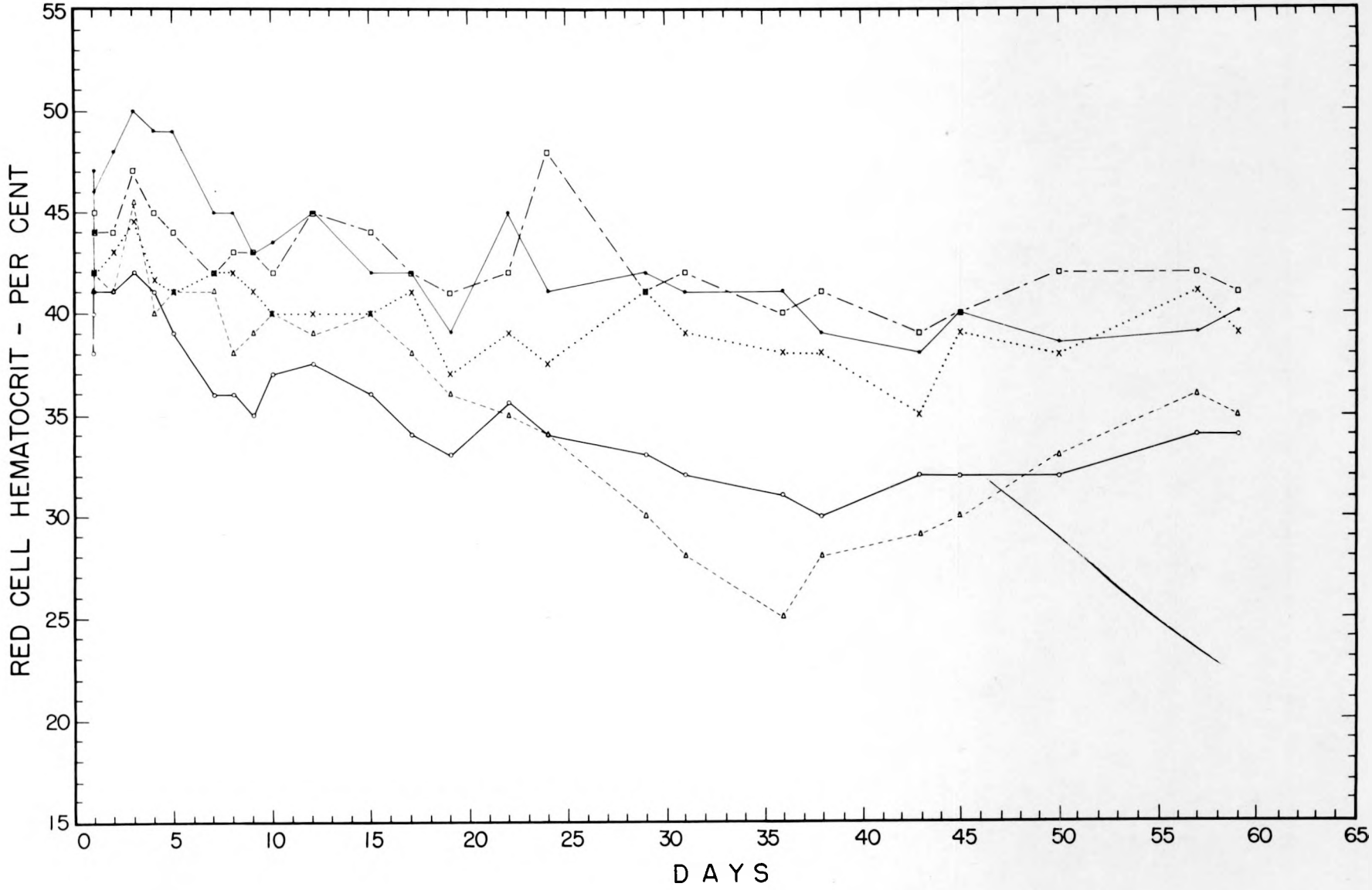

RED CELL HEMATOCRIT - PER CENT
55
50
45
40
35
30
25
20
15
0
5
10
15
20
25
30
35
40
45
50
55
60
65
DAYS

Figure 5

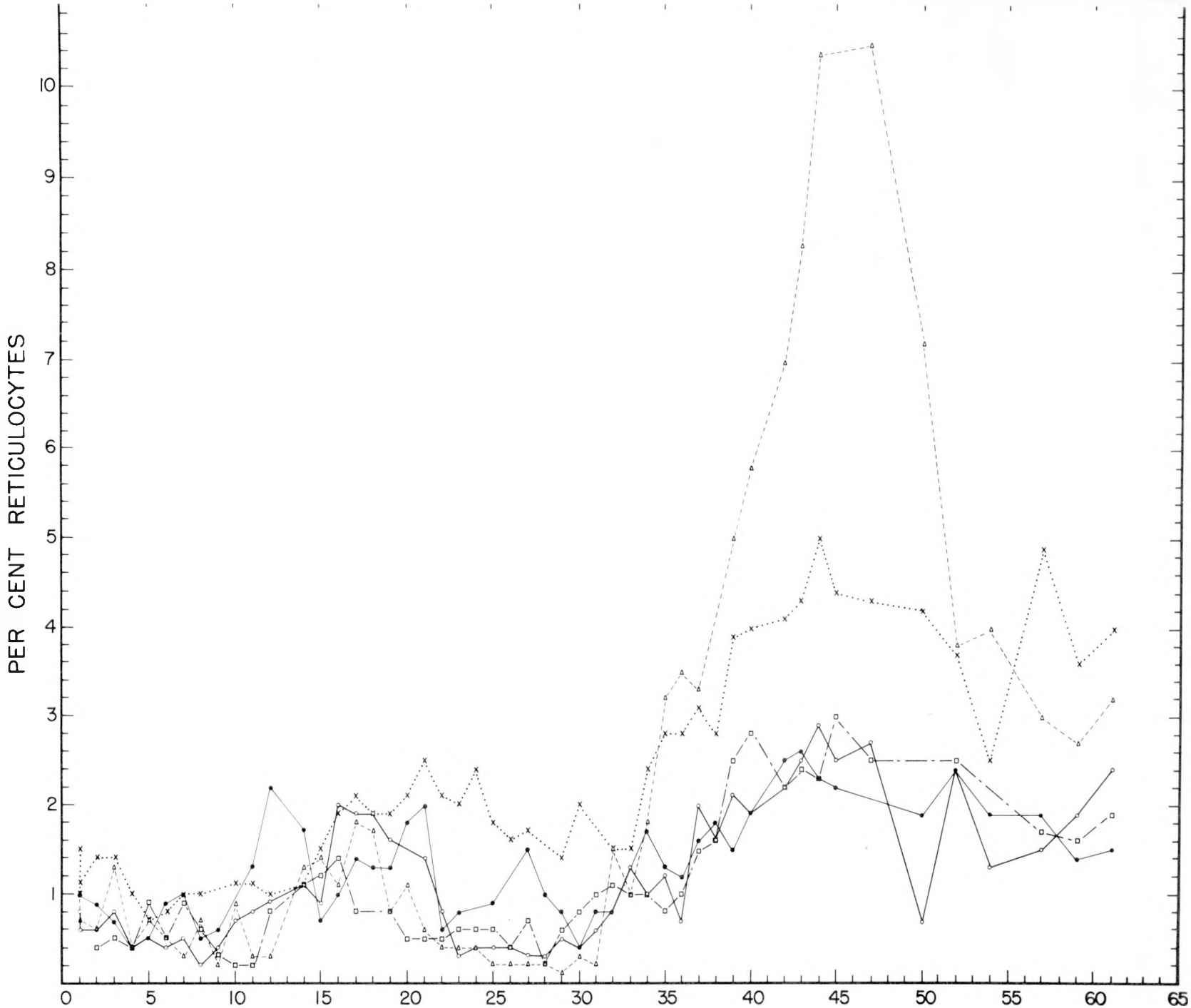
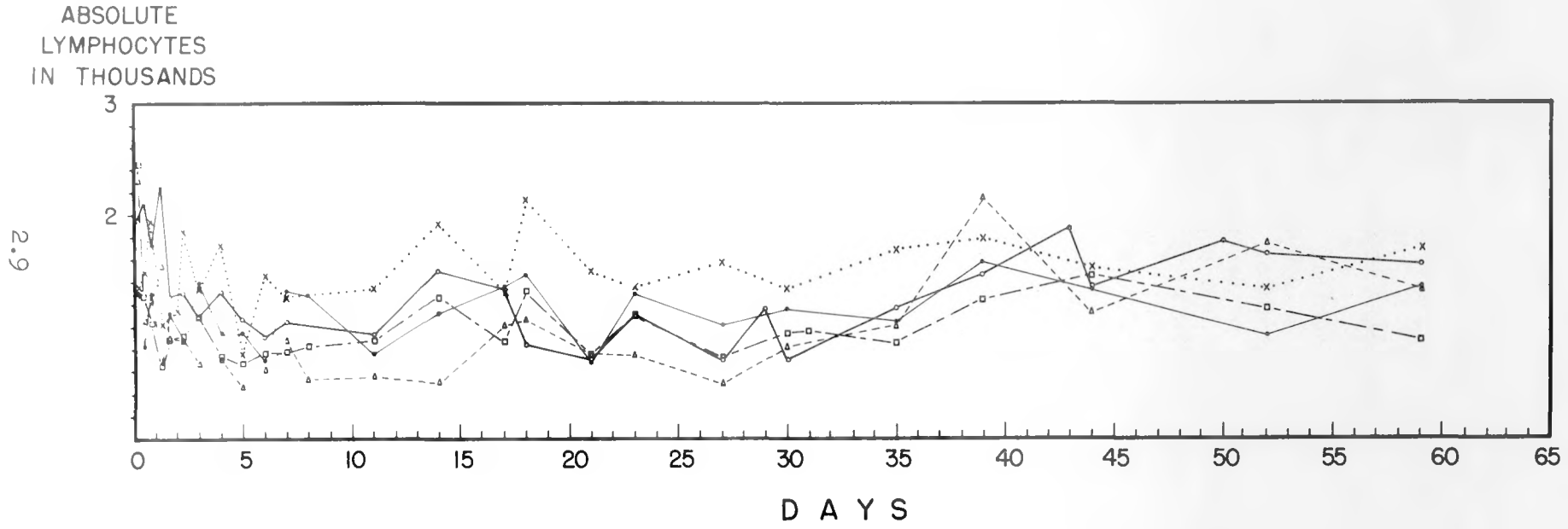

PER CENT RETICULOCYTES
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50
55
60
65
DAYS

Figure 6


ABSOLUTE
LYMPHOCYTES
IN THOUSANDS
3
2
0
5
10
15
20
25
30
35
40
45
50
55
60
65
D A Y S

2.9

averages. One had a leukocytosis of 17,350. This patient's highest pre-exposure W.B.C. had been 12,500. The total white count stayed at high normal values for two days and then decreased until about the 9th day. Between the 9th and 16th days there was a slight rise in the total white count. Abnormal large and hypersegmented neutrophils contributed to this cell population significantly. After the 15th day there was a gradual fall in the total white count until the 23rd day, from a low normal to definitely subnormal levels. On about the 22nd day a more rapid fall of total white count began, particularly in patients A and C, the two with the highest radiation dose. These two men reached the lowest value at the 29th and 30th day, and subsequently showed a rather rapid recovery. The three men with slightly lower radiation doses reached their lowest white cell values at a slightly later time, from the 33rd to the 36th day, and then began to recover. During the period of lowest total leukocyte count the differences among the patients depended chiefly on differences in neutrophil levels; there was very little difference in the absolute lymphocyte count. For example, 31 days after exposure patient A had a leukocyte count of 1,150 with 80 per cent lymphocytes while patient E had a leukocyte count of 3,150 with 31 per cent lymphocytes. It is interesting that the two men with the highest radiation dose, whose white counts reached the lowest levels, showed a more energetic recovery phenomenon, and around the 50th day had the highest white counts of the group.

Lymphocytes. During the first 48 hours the decrease in lymphocytes contributed significantly to the changes in the total white count. After that time the chief factor was the variation in the number of neutrophils.

Most of the decrease in lymphocytes occurred during the first 48 hours, to an average value of about 1,000, but slightly lower values were reached on about the 5th day. After the initial decrease in numbers, the lymphocyte levels tended to stay quite stationary, with a slight increase toward normal after about 30 days. The lowest lymphocyte values were reached by patient A, who had the highest radiation dose. His values fell to about 500 on one occasion and remained below 800 during the most of the first month. However, in patients B through E there did not appear to be a definite correlation between degree of early lymphocyte depression and severity of the later granulocyte depression.

Thrombocytes. Platelet levels may also have shown an initial rise as a result of the radiation, but there is no direct evidence on this point. They tended to remain rather stationary until about the 15th day and then fell progressively, reaching low levels between the 25th and 35th days. The two men with the highest radiation dose reached the lowest values, and patient A, with the highest dose of all, showed a pronounced rebound effect and reached high platelet levels between the 40th and 50th days. The thrombocytopenia correlated with the clinical symptoms of hemorrhagic tendency noted in these patients.

Red Cell Values. The hemoglobin and hematocrit determinations correlate very well with each other and there was no significant change in mean corpuscular hemoglobin concentration during the period of study. Initial fluctuations in these red cell values may have been related to variations in the state of hydration of the patients. The two patients who received the highest dose of radiation showed definitely lower red cell values after the 20th day and both became significantly anemic; the other three developed only a very mild anemia. The lowest values for the red cells were reached between the 35th and 45th days. Some contribution may have been made to the anemia by the withdrawal of significant amounts of blood for various studies.

The values for the reticulocytes were of considerable interest. There was some fall in reticulocyte levels during the first eight days, but they never reached zero. There was an abortive rise in reticulocytes between the 13th and 25th days, and then a distinct rise after the 30th day, reaching a peak around the 45th day. It is interesting that the highest reticulocyte value occurred in the patient with the highest radiation dose.

Morphologic Changes in Blood Cells. Significant changes were seen in the blood films in the five high-dose patients. Within the first few hours there were degenerating white cells of various types, many of them apparently granulocytes. Atypical cells made their appearance and many of these were difficult or impossible to classify. These cells never made up more than a small percentage of the total white cells, however.

Within the first few days, young and "toxic" monocytes appeared. These abnormal monocytes persisted for many weeks. Some of them had irregular or lobulated nuclei.

Young lymphocytes and lymphocytes with dark blue cytoplasm - "irritation forms" - were present within a few days and persisted for a considerable period of time. Some lymphocytes with fissured nuclei were seen, but binucleate forms were not found among the numbers of cells counted; further studies on concentrated buffy-coat preparations are to be reported. Occasional lymphocytes were seen with peculiar large solitary cytoplasmic bodies. There were also lymphoid and monocytic cells with endothelioid characteristics.

One of the most interesting cell types was the giant granulocyte. In addition to the large size, some of these granulocytes showed hypersegmented nuclei, and some showed small nuclear projections. These cells began to appear within three or four days and were seen in all the patients about the end of the first week. Within a few days they became less plentiful and they were not prominent after the first five weeks. During the recovery phase toxic granulation of the neutrophils was prominent and an occasional nucleated red cell was seen.

Bone Marrow. Serial studies of aspirated bone marrow were performed. The marrow was aspirated from different sites, usually from the iliac crest or posterior iliac spine. The possibility of aspirating several different sites simultaneously in the same patient to determine whether there was uniform damage to the bone marrow in various areas was considered. However, it was believed that the radiation dose was fairly uniform and that there would probably not be any important difference in the dose to the marrow that could be related to the position of the person in relation to the source of the radiation. The sites of aspirations were recorded; no important effects related to location have been noted.

The first marrow was aspirated about 12 hours after the accident. There were no clear-cut abnormalities seen at this time. Some of the specimens seemed somewhat more cellular than normal with prominent clumps of fibrils and stromal elements. In two samples there were some abnormally large granulocyte precursors. The average erythrocyte-granulocyte ratio for all five specimens was 0.42. The second bone marrow obtained two days after the exposure was quite similar; however, by this time the E.G. ratio had dropped to 0.26. In three of the five specimens the megakaryocytes seemed somewhat more numerous and some of them showed slight abnormalities of morphology. Giant neutrophil precursors were now quite definite. The bone-marrow samples on the 3rd and 4th days showed some mild decrease in cellularity. The number of megakaryocytes by this time was normal or decreased and the morphologic abnormalities were more prominent. This included the presence of degenerating megakaryocytes and of small and immature forms. The E.G. ratio was 0.22 on the 3rd day and 0.28 on the 4th day. These ratios are based upon study of only two patients on the 3rd day and three patients on the 4th. On the 5th day only two patients had marrow samples. These showed a further depression in E.G. ratio with an average of 0.19. The megakaryocytes showed increasingly severe abnormalities in morphology. All five of the patients were subjected to bone-marrow studies on the 9th, 16th, 24th, 29th, 39th, and 54th days. On the 9th day total cellularity was very much diminished. Megakaryocytes were distinctly decreased in number and morphologic abnormalities of the megakaryocytes were very striking. The E.G. ratio was 0.32. On the 16th day there was a further relative depression of granulocytes with the E.G. ratio now 0.62. Megakaryocytes were very much diminished in number and had severe degenerative changes. On the 24th day the marrows reached a severe degree of hypocellularity and megakaryocytes were at their lowest ebb. Degenerating forms were again prominent. By this time the granulocyte forms were still further depressed and the E.G. ratio was 2.24. On the 29th day the E.G. ratio was 1.26; the cellularity appeared less depressed and the megakaryocytes were more plentiful than on either the preceding (24th) day or subsequent (39th) day observations. On the 39th day the marrows were exceedingly hypocellular. Megakaryocytes were diminished or absent, but degenerating forms were no longer plentiful. The E.G. ratio was 1.36. On the 54th day cellularity was back to normal or even increased. The number of megakaryocytes was near normal. The E.G. ratio was 0.65.

The presence of the giant neutrophils was questionable at 12 hours, definite at 24 hours, very prominent at the 3rd, 4th, 5th, and 6th days, and less prominent at the 9th day. These forms were still present at the 16th day, but had virtually disappeared by the 24th day.

At no time were the bone marrows characterized by great prominence of degenerating cells. There were, however, some degenerating cells in the early marrow specimens. These became less plentiful and again were noted to be prominent around the period of hypocellularity at the 29th day. Lymphocytes seemed to be relatively more prominent in the marrows obtained between the 4th and 9th days than they were earlier or later. Plasma cells showed some relative increase at the 5th and 9th days, but never reached strikingly high figures. Eosinophils were persistently present. The absolute variation in their numbers is difficult to estimate.

In summary, the bone marrows showed an initial dip in cellularity during the first three days, and then a gradual further diminution with some fluctuation but reaching a maximum hypocellularity at the 39th day. Following this there was rapid regeneration to normal or increased cellularity by the 54th day. During the first three days after radiation there was a slight relative diminution in red cell precursors maximal at about the 3rd to 5th day. Then there was a pronounced depression of granulocytes, so that on the 24th day the number of granulocytes was exceedingly small. During the 2nd to 16th days giant abnormal neutrophil precursors were present. These were most prominent at about the 4th to 9th days. Degenerating megakaryocytes were prominent during the 5th to 29th days, and the total number of megakaryocytes reached the lowest level at about the 24th day.

Hematologic Values for the Three Men with Low Radiation Dose

The three patients with low radiation doses had also had multiple routine blood counts over a period of years before the accident. One of them (G) had shown a mild leukocytosis with neutrophilia on various occasions, once as early as 1951. Subsequent to the irradiation exposure this patient showed a variable leukocytosis, the white count reaching 21,000 on one occasion but usually varying between 9,500 and 17,000. Bone-marrow studies on several occasions after the exposure showed a persistently hypercellular marrow with granulocyte predominance. There was no evidence that these abnormalities could be related to the irradiation but the possibility has been considered that they might indicate a pre-existing disorder. The blood studies done during succeeding months after the exposure showed no evidence of progressive abnormality and the phosphatase level in the granulocytes, determined several months after the accident, was normal.

These men were not studied at the ORINS Medical Division until the second day after the radiation exposure. Patients F and G had blood

counts at the Y-12 dispensary the first day after exposure and patient H had, in addition, a blood count on the day of exposure. Some of these blood films were available for later review. After the second post-exposure day, all three were followed closely with blood and marrow studies done at the ORINS laboratory.

The findings in these three low-dose patients can be summarized with the statement that there are no definite changes clearly attributable to radiation. Patient F had lymphocyte values that stayed above 2,000 and no clear pattern of radiation effect was seen. Patient G, previously mentioned as having unexplained leukocytosis, had his lowest lymphocyte value, 1,220, on the 3rd postirradiation day. His total white count fluctuated greatly, reaching 21,000 on the 4th postexposure day. Patient H, with the lowest radiation dose, had for some reason a mild relative lymphocytosis two to four weeks after the exposure.

Discussion

The hematologic values in the five higher-dose patients demonstrate the expected pattern and emphasize that total-body irradiation in man produces a very clearly defined syndrome. The blood and marrow changes become apparent during a period of several weeks. There are certain clearly defined stages: early and persistent lymphopenia and variable transient leukocytosis; mild leukopenia during the first 10 days; abortive rise in white cells and some increased erythropoiesis at about two weeks; subsequent severe depression of neutrophils and platelets, greatest at four to six weeks; rapid recovery of platelets and neutrophils; and anemia maximal at about seven weeks, with recovery accompanied by reticulocytosis. It is our impression, on the basis of these and other reported data, that this sequential pattern is rather uniform in different persons exposed, and that a similar pattern occurs after radiation over a rather wide range of dose. The time required for development of the marrow depression and recovery from it is much longer in the human being than in small experimental animals but the sequence of events is similar.

Early lymphopenia is a valuable prognostic sign. Bone-marrow studies performed by ordinary methods during the first few days may be misleading in that they may show very little obvious abnormality even after high radiation dose. Reticulocyte counts do not appear of much value in making an early judgment of the severity of radiation damage.

The tendency for spontaneous hematologic recovery in these patients was most impressive, and justifies the use of conservative therapy in patients whose radiation dose is believed to be in a definitely sublethal range.

Acknowledgements

The authors wish to thank Dr. C. R. Sullivan, Jr., and the staff of the Y-12 dispensary laboratory for the blood values reported here. Dr. Eugene Cronkite gave much valuable help during the period shortly after the accident, and assisted in improving the platelet counting technique in our laboratory. Dr. William Moloney provided the alkaline phosphatase determination on the blood of patient G.

The charts were drawn by Miss Alice Keene. Mr. Bill Jones helped with the collection of data.

Table 1

Average Blood Values Preceding Exposure

PATIENT	A	B	C	D	E
No. of Determinations	6	8	4	6	4
Average Hemoglobin (g)	14.6	15.3	13.0	13.9	14.3
Average W.B.C.	8,525	7,300	10,963	8,117	6,850
Average Lymphs/cu mm	2,595	2,785	4,354	3,580	2,078
Average Differential:	%	%	%	%	%
Lymphocytes	31.0	37.9	39.75	43.0	30.5
Neutrophils:					
Segmented	63.0	59.4	56.75	52.0	64.0
Unsegmented	1.5	.4	.25	.5	.8
Monocytes	.75	.6	1.75	1.5	1.5
Basophils	.25	1.7	--	--	.5
Eosinophils	3.5	--	1.5	3.0	2.5

Table 2

Blood Values Approximately 1½ Hours After Exposure

PATIENT	A	B	C	D	E
R.B.C. (in millions)	5.50	5.50	4.69	5.11	4.81
W.B.C. per cm mm	9,050	8,250	17,350	10,450	11,400
Lymphocytes per cu mm	2,370	1,320	1,995	1,358	2,451
Differential:	%	%	%	%	%
Neutrophils:					
Segmented	64.5	74.5	73.5	69	70
Unsegmented	5	2.5	9.5	8.5	3
Lymphocytes	25.5	16	11.5	13	21.5
Monocytes	3.0	6.0	5.0	6.0	2.5
Basophils	0.5	0.5	--	1.0	--
Eosinophils	1.5	--	0.5	2.5	3.0
Other	--	0.5	--	--	--

SPECIAL HEMATOLOGIC STUDIES ON RADIATION CASUALTIES IN THE Y-12 ACCIDENT

Progress Report

E.P. Cronkite*, T.M. Fliedner*, V.P. Bond*
G.A. Andrews** and A.M. Johnson**

Tritium-labeled thymidine (H^3Th), a specific precursor of DNA, has been used to study the kinetics of hematopoietic cell turnover in human beings (1). After injection of the material, labeling of hematopoietic precursor cells in the bone marrow occurs within minutes, followed by progressive labeling of mature elements in the peripheral blood. Labeling of bone marrow cells also is marked after one hour of incubation in vitro with H^3Th (2), and it has been demonstrated with the in vitro technique that a small percentage of mononuclear cells circulating in the peripheral blood of normal human beings have the capacity to synthesize DNA, and thus probably are destined to divide again (3). Earlier radiation protection studies (4,5), extensively reviewed (6), had indicated that there is either a pool of primitive pluripotential cells or diverse stem cells (1,2,7,8), some of which must be circulating. Such a pool of cells is consistent with the earlier beliefs of Pappenheim and Ferrata (9,10). It is possible that the radiation protection cells are among the family of DNA synthesizing cells described in normal human blood (2,8). Total-body irradiation of animals alters the number of labeled cells in the bone marrow and peripheral blood, and the time sequence of these changes has been described for the bone marrow of the rat (11) and dog (12), and for the peripheral blood of the dog (12). The Y-12 accident afforded the opportunity to observe the time sequence of changes in the proliferative potentials of bone marrow and blood cells of irradiated human beings, as well as to follow the mitotic index of the marrow and the morphological appearance of both bone marrow and peripheral blood cells.

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* Medical Research Center, Brookhaven National Laboratory, Upton New York
** Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee

Details of the accident, and estimated doses received are given in other sections of this report. It was not possible to obtain bone marrow and blood samples for these studies earlier than 2½ days after the accident, and observations on the time period up to 4½ months are included in the present report. Data on eight patients, five of whom received of the order of 230 to 360 rads, and three of whom received from 22 to 69 rads, are included. The material obtained has not been evaluated completely as yet because of the large amount of time required to process autoradiograms, to do quantitative counts on the slides, and to evaluate the results.

In addition to the studies indicated, platelet counts and in vitro thymidine incorporation studies on peripheral blood were done at the Y-12 Dispensary on a group of "exposed" and unexposed comparison persons.* The "exposed" persons were in the building in which the accident occurred at the time it happened. The doses received by these persons cannot be assessed at present with any degree of accuracy by physical means; however it is probable that none received more than 5 r and most probably received a fraction of a roentgen.

Methods and Materials

Studies on Proliferative Capacity of Marrow and Blood Cells. Marrow suspensions were collected in tubes containing either 1 per cent Na_2 EDTA or heparin as the anticoagulants, and H^3Th (0.5 microcuries per milliliter). The mixture was incubated for one hour at room temperature (2).

Leukocyte concentrates of blood incubated one hour with H^3Th were made by sedimenting the red cells with a dextran-EDTA mixture. The supernatant plasma was aspirated; and the white cells were packed by centrifugation. They were then resuspended in enough plasma to make a concentration of $10^5/mm^3$. Autoradiograms were made by means of the stripping film technique described by Doniach and Pelc (15). British Kodak AR-10 stripping film was used. Autoradiograms were stained with Wright's or Giemsa stain.

Mitotic Index. The mitotic index was determined by a modification (13) of the marrow squash technique of Ford and Hammerton (14). The marrow suspension immediately after aspiration was introduced into hypotonic citrate for 10 minutes and then centrifuged. The sediment was fixed (acetic acid-ethyl alcohol-glycerine) and then stained with Feulgen's stain. Squash preparations were made and the number of mitoses per 1000 nucleated cells was tabulated. The cell line cannot

* The authors are indebted to Drs. C.R. Sillivan, K.S. Lane and M. Brucer, and to Mr. C. Brewster for their aid and cooperation in performing these studies.

be determined by this method. At least 3000 cells were counted in each preparation.

Platelet counts were done by direct phase microscopy (16) on 14 "exposed" and 14 unexposed persons on the 30th postexposure day at the Y-12 Dispensary. In vitro blood studies were performed on 15 "exposed" persons during the first four weeks, approximately two times per week. Comparison studies were done at one time only on 15 unexposed persons.

Results

Proliferative Capacity of Bone Marrow. As indicated previously, studies were not performed in the first 2½ days at the time when animal experimentation indicates maximum depression (11,12). The early bone marrow smears were consistent with increasing hypoplasia of the marrow and apparent morphologic abnormalities. Remaining cells in both the erythroid and myeloid series were found to be labeled; however, the percentage of labeled cells was less than normal. Insufficient counts have been completed; however, it appears that the results will be consistent in general with those obtained in animals (11,12).

In Vitro DNA Synthesis by Mononuclear Blood Cells. The serial studies are still incomplete. The sequence of events within the first week after the accident in the high-dose group is shown in Fig. 1. The line drawn indicates the approximate time course of change obtained in total-body irradiated dogs in the low lethal range. So far as studies have gone the depression in the number of DNA synthesizing cells and the recovery phase in the patients parallels the results obtained in the irradiation of dogs.

Mitotic Index. The results are shown in Fig. 2, with estimates of the radiation doses received given in the figure caption. The mitotic index of normal bone marrow is about 1 per cent (13,17). When first studied (4th day) all the exposed men in the heavy-exposure group showed a depression in the mitotic index. This was followed by a probable increase on the 8th day with a secondary fall by the 16th day. Thereafter the counts rose progressively to normal by the 29th day. When last studied at 4½ months, the counts were significantly above normal. In the three men who received of the order of 20 to 60 rads, the depression at four days was slight. The counts were within normal limits at all later times studied.

Photomicrographs of mitotic figures of squash preparations are shown in Fig. 3. The squash preparations of the heavy exposed men showed abnormal mitoses with chromosomal stickiness, bridges, and clumping between the 4th and 16th day after exposure (Fig. 3, f to i). Whereas the chromosomes of normal mitotic figures spread out easily, it was most often impossible to "squash" these disturbed mitoses.

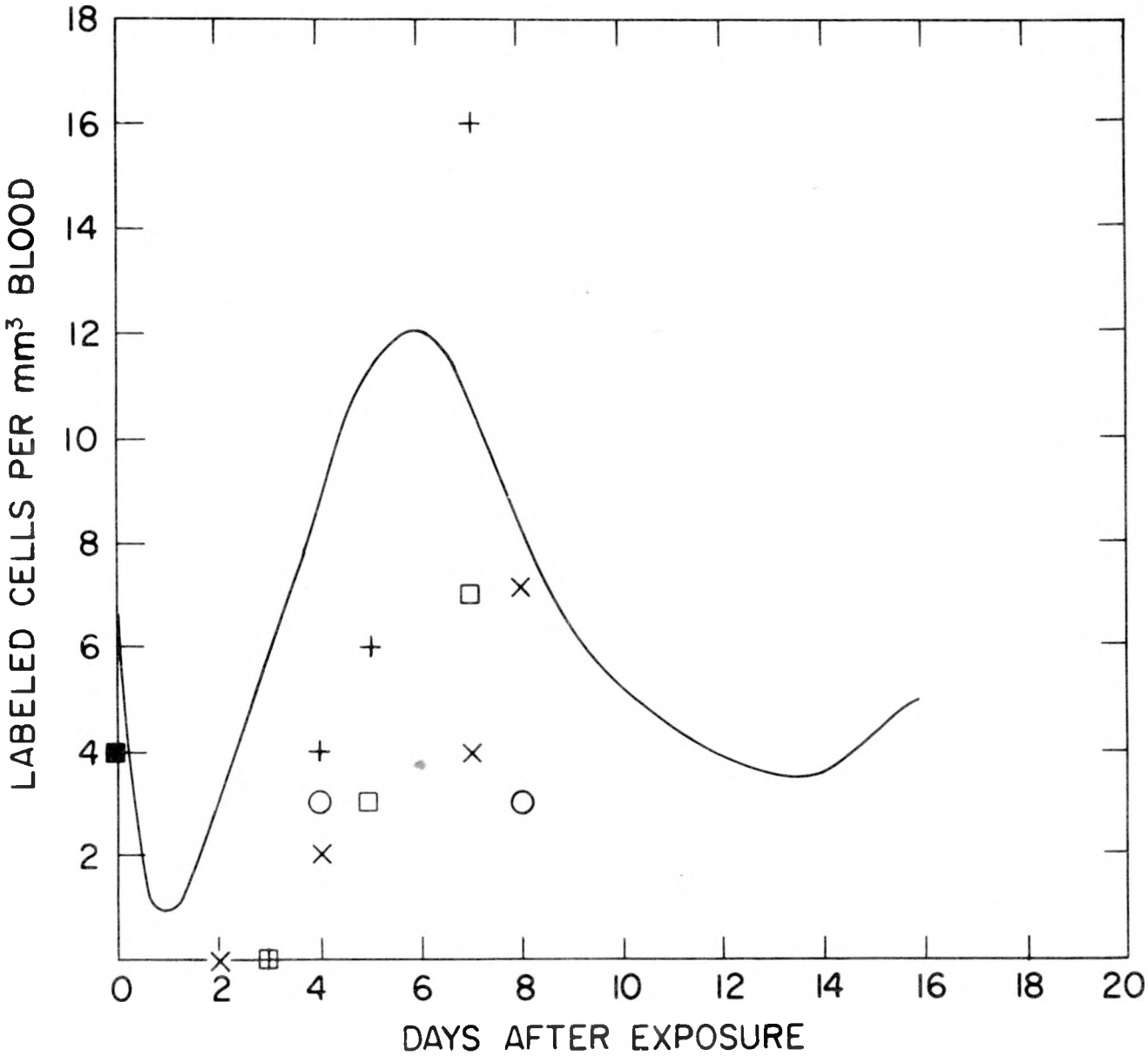

Figure 1. The sequence of changes in the number of DNA synthesizing mononuclear cells in the peripheral blood of the heavily exposed patients. Patients corresponding to the symbols are as follows: X : D; ○ : A; □ : B; + : C. The superimposed curve approximates the sequence of changes of the numbers of similarly labeled cells in the blood of dogs exposed to total-body radiation in the low lethal range (actual number of cells in dog blood is 10 times that indicated on the scale).

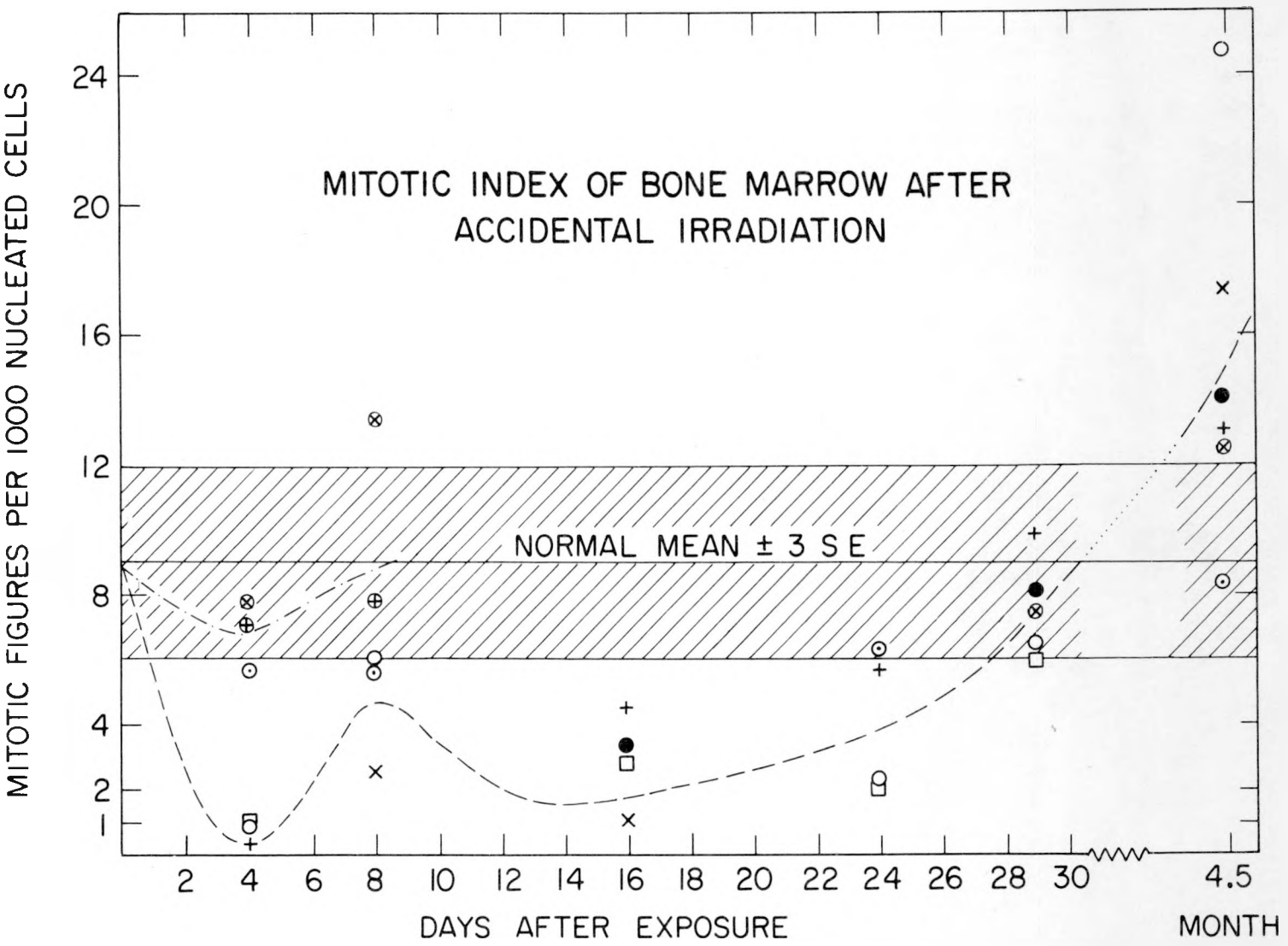

Figure 2. Mitotic index of exposed individuals as a function of time after exposure. Patients corresponding to the symbols, and approximate radiation doses received are as follows. ● A 365 rads; + B 270 rads; X C 339 rads; ○ D 327 rads; □ E 236 rads (high dose group); ⊙ F 68.5 rads; ⊗ G 68.5 rads; ⊕ H 22.8 rads (low dose group).

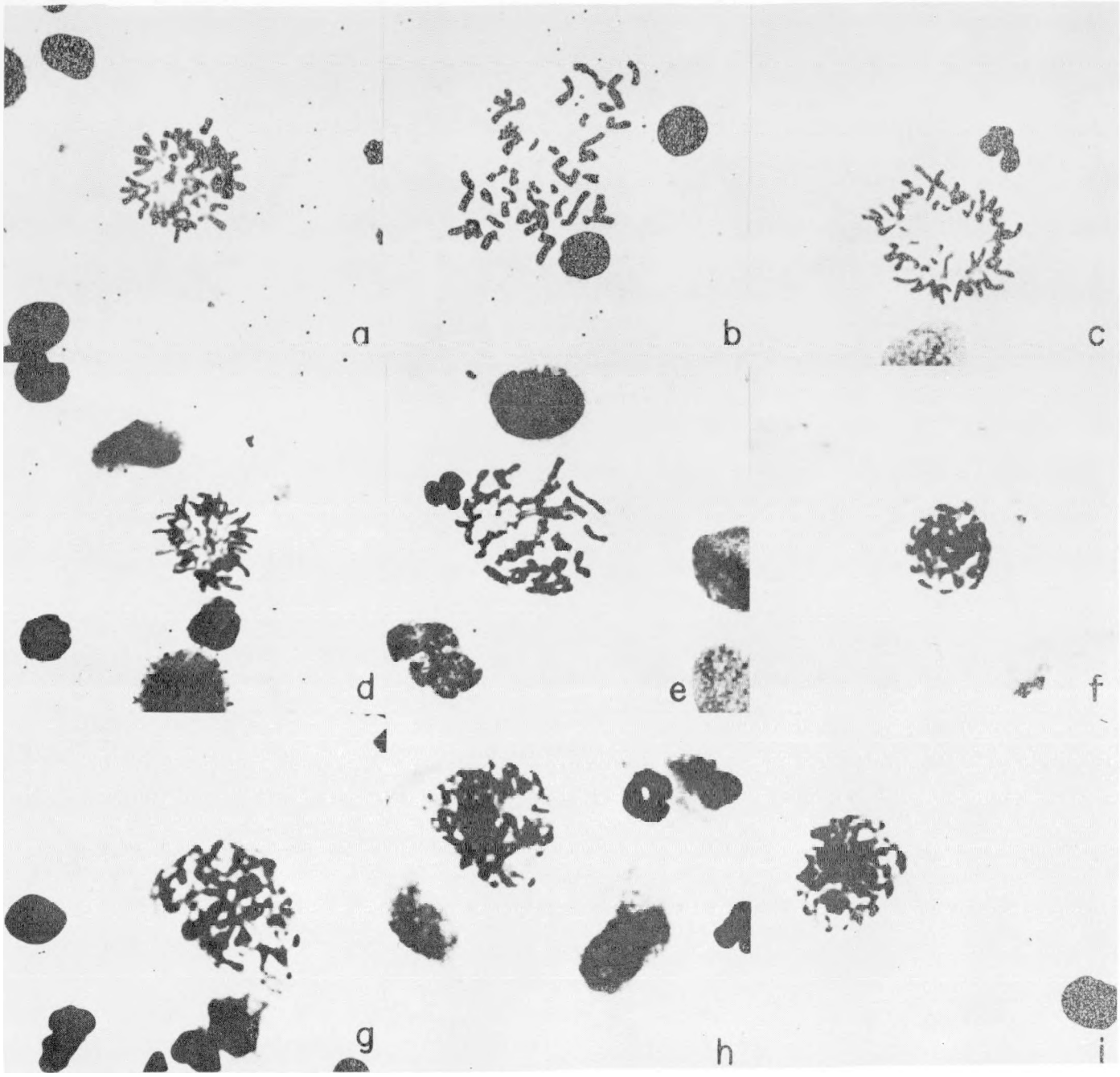

Figure 3. Mitotic figures in Feulgen-Squash-Preparations of human marrow. a to e: Mitoses in normal human bone marrow, f to i: mitoses in bone marrow of men accidentally exposed to ionizing radiation in the order of 236 to 365 rads, 16 days after exposure.

We acknowledge the superb photomicrographs of Mr. Robert S. Smith, Photography Department, Brookhaven National Laboratory.

A marked difference in the degree of change in mitotic index was evident between the high- and low-exposure groups. The mitotic index on the 4th day is plotted against dose in Fig. 4. The results suggest that a good correlation may exist between dose and the degree of mitotic depression.

Platelet Counts on Low Dose Dispensary Group. The results of platelet studies on the 14 patients of the very low-dose group are presented in Table 1 as the number of platelets counted per hemocytometer chamber. These numbers can be converted to platelet counts per cubic millimeter by multiplying by 5000. It is quite evident that there is no significant difference between the two groups. Results of the in vitro labeling studies were not evaluated at the time of this report.

Discussion

It is premature to discuss these results in detail since material for many more time intervals are yet to be studied. However, it is worthy of comment that as far as the observations have been made there is a good parallelism between the studies on irradiated dogs and these human beings in respect to circulating peripheral blood cells and bone marrow cells that synthesize DNA. Evidence from animal work (11,12,18) indicates increasingly that irradiation probably has little effect on the actual process of DNA synthesis, and that apparent changes in DNA synthesis reported (using standard biochemical procedures) result principally from mitotic arrest or cell death, leading to a changing cell population, or diminished numbers of cells after exposure. The technique of autoradiography used in these studies obviates to a degree these difficulties since DNA synthesis in individual cells can be determined; however, the interpretation of the results is difficult because of the loss of cells from the marrow after exposure; this loss is difficult to quantify. It is possible that the changes in the number of circulating labeled cells may be correlated with periods of degeneration and regeneration, or attempted (abortive) regeneration.

The degree of depression of the mitotic indices in the first few days after exposure appeared to correlate well with the physical estimates of dose received. Significant changes in mitotic index and disturbance in the morphologic appearance of the mitotic figures would be expected from previous work on animals (19-24). This procedure, then, which can be completed within eight hours after the marrow is drawn if necessary, might be developed to serve as a useful early index of the degree of exposure. It is felt that the optimal times to study these early changes in the mitotic index would be 1 to 3 hours, 3 to 12 hours, 18 to 24 hours, and three days to establish the course of decrease. It should also be pointed out that the transient small rise in the mitotic index on the 7th and 8th days may be significant. It is at this time that many large hypersegmented neutrophils appeared in the

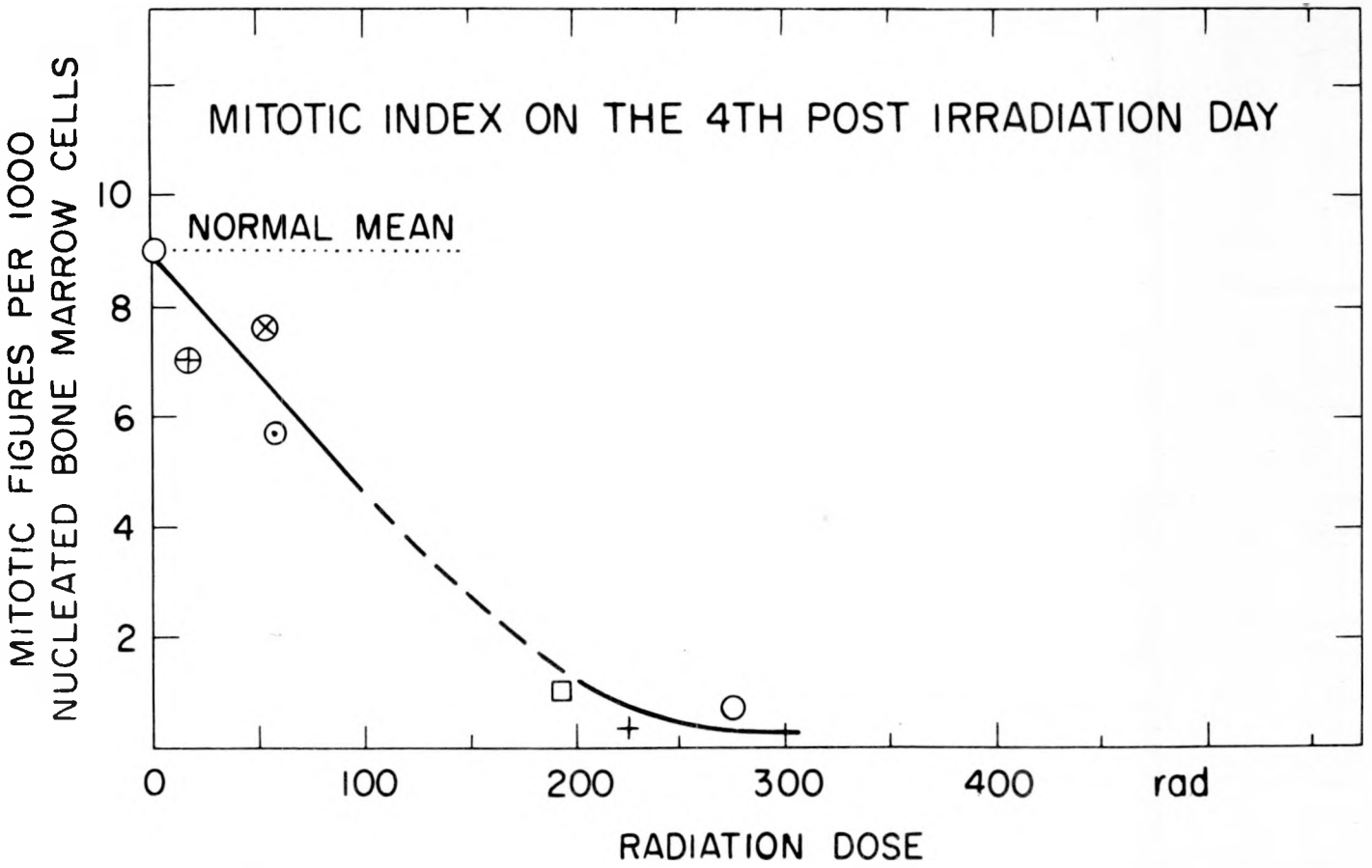

Figure 4. Mitotic index of exposed individuals on the 4th postirradiation day as a function of the various doses. Patients corresponding to the symbols as shown in Fig. 2.

peripheral blood, and the rise in mitotic index may correspond to the time of an abortive attempt at regeneration of disturbed cell generations.

Of more than casual interest is the apparent increase in mitotic index at $4\frac{1}{2}$ months, for which alternative explanations are possible. Turnover time (T) for a proliferating tissue in a steady state can be expressed as a function of mitotic index (M_I) and mitotic time (t_m), or

$$T = \frac{t_m}{M_I}$$

From the peripheral blood concentrations, as an index of recovery, it appears that by $4\frac{1}{2}$ months, equilibrium has been reestablished. Thus one can deduce that the average turnover time for all marrow elements probably is significantly reduced even after five months when one assumes mitotic time to be the same before and after irradiation. If one assumes that the original proliferating marrow mass has been reconstituted, then one must conclude that the more rapid turnover indicates imperfect proliferation with loss of about two out of three cells in the marrow before maturation and release into the peripheral blood or that maturation and release is undisturbed but the life span is diminished. An alternative explanation is that the original mass of the proliferating marrow has not been reconstituted and that a smaller mass of marrow is working faster to maintain the normal cell level of the peripheral blood. At the present time it is not possible to evaluate these alternative explanations. However, one might be inclined to favor the former since imperfect populations of cells are seen during the abortive rises.

The failure to detect a change in platelet count in the 14 persons in the building at the time of the accident indicates after four weeks that only a small dose, if any, was received. It cannot be stated what might be the lowest dose detectable in a group this size. A significant drop in average platelet count was found in a group of 137 Marshallese people exposed to an estimated 14 r of fallout gamma radiation (25).

Acknowledgment

The authors are indebted to Dr. M. Brucer, Dr. B. W. Sitterson and Dr. A. L. Kretchmar, Medical Division, Oak Ridge Institute of Nuclear Studies, for their cooperation and encouragement in making these observations possible.

TABLE 1

Comparison of Platelet Counts in Low-Dose Exposure and Comparison Nonexposed Group. Number of Platelets per Hemocytometer Chamber

Comparisons		Exposed
Mean	52	51
Standard Deviation	12.4	10.9
Range	35-84	37-74
Number of Persons	15	14

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BIOCHEMICAL STUDIES

Arthur L. Kretchmar, M.D.

The accidental exposure of eight normal persons to significant total-body irradiation has made available material that can give important clues to the metabolic effects that irradiation produces in man. Studies of this material are still in progress and this is only a preliminary report of these studies.

Blood Changes. The serum uric acid did not change after exposure (Fig. 1). Although the initial value (approximately 24 hours after exposure) was higher than any subsequent value, it was not an abnormally high level. The results of plasma α-amino nitrogen determinations (1) are shown in the same graph (Fig. 1). There are no significant variations in any of the five men. Breakdown of damaged cells might be expected to release uric acid precursors and amino acids. The methods are too crude or the changes are too small to be detected in these patients.

Serum transaminase and lactic dehydrogenase activity was not affected by the exposure. This observation is consistent with the results of studies in rabbits reported by Brent et al. (2).

No significant alterations occurred in serum electrolytes. It seems likely that this is because vomiting and diarrhea were mild or absent and secondary electrolyte imbalance did not occur.

There was no change in serum cholesterol, blood sugar or NPN. Considering the good nutritional and clinical condition of these men, this is not surprising.

Changes in Urinary Excretion. The 24-hour urine volume did not show a systematic change in all the men. This is shown in summary form in Fig. 2. The volumes of the first four consecutive 24-hour collections were measured, the results were averaged, and the average was plotted in Fig. 2 as "period I." Consecutive four-day periods are plotted in the same way. The volume was usually greater during the 4th through the 12th days after irradiation. Possibly the exposure had a mild diuretic effect in these men as has been frequently observed after irradiation of animals.

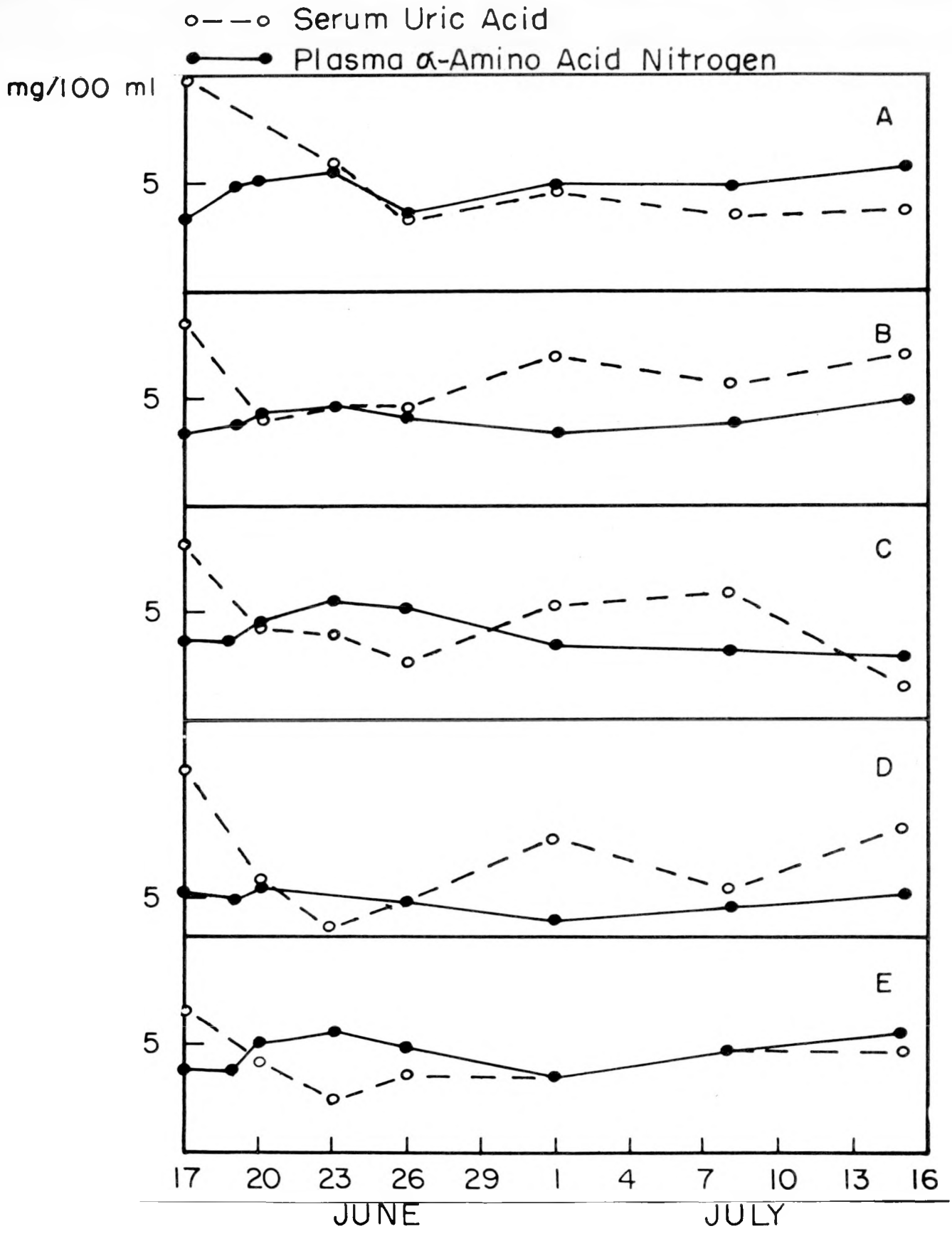

Figure 1. Serum uric acid and plasma α-amino acid nitrogen in samples taken from five accidentally irradiated men. The irradiation occurred on June 16. The first sample was obtained approximately 12 hours after the accident.

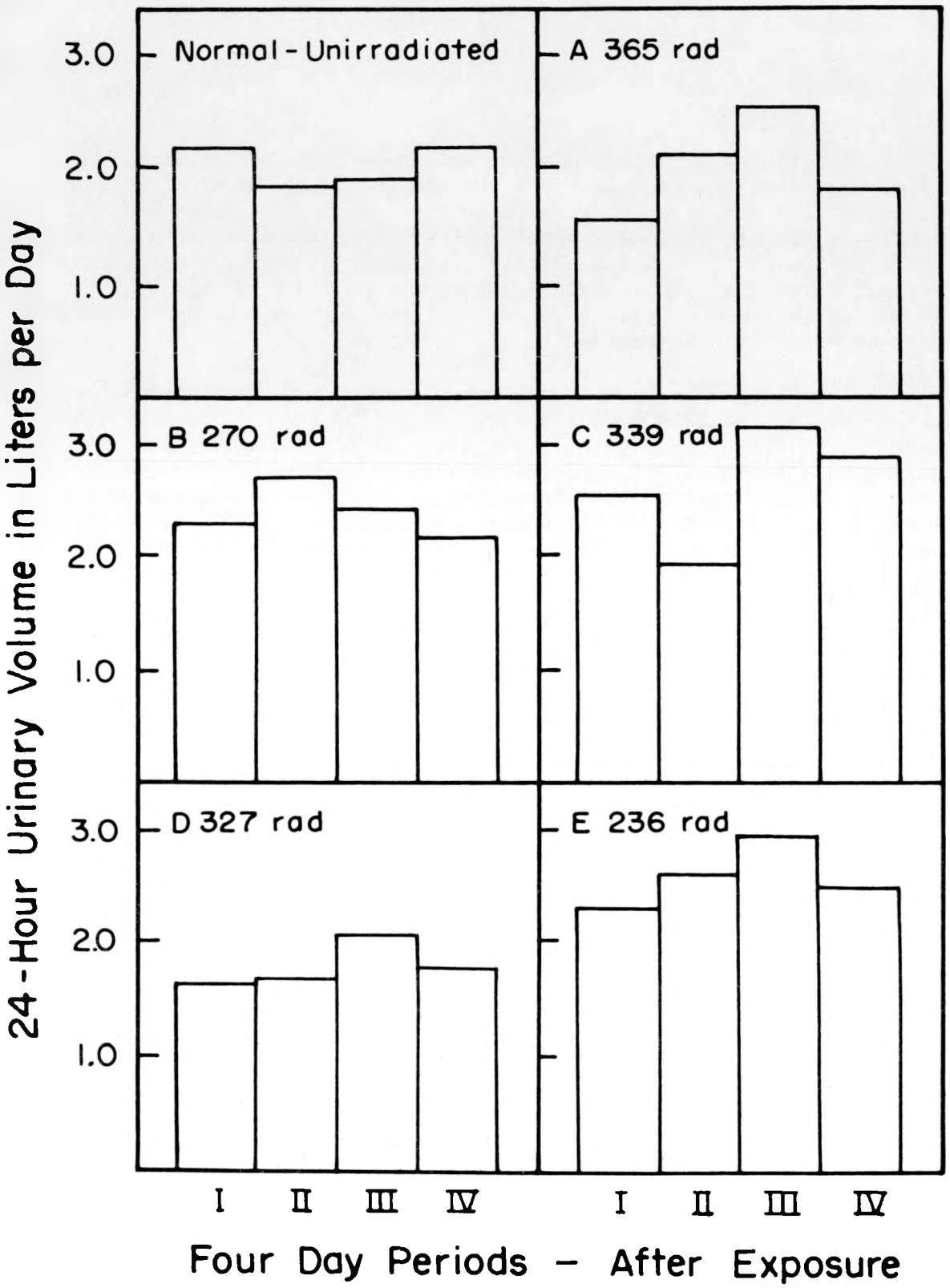

Figure 2. Volume of urine excreted by five accidentally irradiated men. The first 16-day interval that followed irradiation has been divided into four metabolic periods of four days each. Each bar represents the average of the volume of the four daily collections that make up each metabolic period. Data from a normal subject on a controlled diet but with unrestricted fluid intake was averaged in the same way and is included in the first chart for comparison.

Creatinine excretion was not influenced by the irradiation (Fig. 3). Creatine excretion was not increased. This is of interest since we have observed creatinuria in a child who was given 800 r of cobalt-60 irradiation. The creatinuria was not observed in a child exposed to 300 r. Both these children had acute leukemia. Creatinuria following irradiation has been reported to occur in animals (3,4,5). It may be that creatinuria regularly follows exposure to higher doses than occurred in this accident.

The total urinary nitrogen was higher during the interval between the 4th and 12th days after exposure (Fig. 4). This corresponds, roughly, to the urinary volume, which was usually slightly increased during this interval. The increased nitrogen excretion may not, therefore, represent an increased formation of nitrogenous waste products. There is no doubt that the irradiation caused tissue effects as other sections in this report show. This is also supported by increased excretion of certain amino acids (to be discussed). If this cell damage is not reflected in increased urinary nitrogen excretion, then intermediate products of nitrogenous catabolism have been reutilized. This could occur because of the relative radioresistance of most tissues of the body. These results are compatible, too, with the view that the most important (quantitatively) effect of irradiation at these dose levels is an inhibition of anabolic processes in sensitive tissues with a relatively less prominent "killing" effect (6).

The lack of any prominent effects in total nitrogen excretion was also observed in uric acid excretion and in the excretion of α-amino nitrogen (Fig. 5). The changes in the latter did not occur in all five patients and could not be correlated with the estimated dose. Three of the patients, however, did show some increase in urinary α-amino nitrogen. There was no aminoaciduria in any of these, since the ratio of α-amino to total nitrogen was not abnormal.

The method used for α-amino nitrogen in the urine (7) is very specific and, therefore, does not measure taurine (one of the four major urinary amino acids) nor does it measure β-amino acids, since the reaction between these and ninhydrin is much slower. The column chromatographic procedure of Moore *et al.* (8), on the other hand, gives precise quantitative results as well as qualitative results that indicate which of 50 or more possible compounds is affected, if any. Preliminary results from the use of this column method are listed in Table 1 and Table 2.

The taurine excretion (Table 1) seems to be elevated in the persons exposed to the highest doses of irradiation. The data are too meager to discuss a correlation between dosage and level of excretion. Patient A, who was exposed to 365 rads of γ and neutron irradiation, excreted more taurine during the 4th day than any of the previous three days and subsequently less taurine was excreted. By the 16th day the excretion of taurine was in the normal range (Fig. 6).

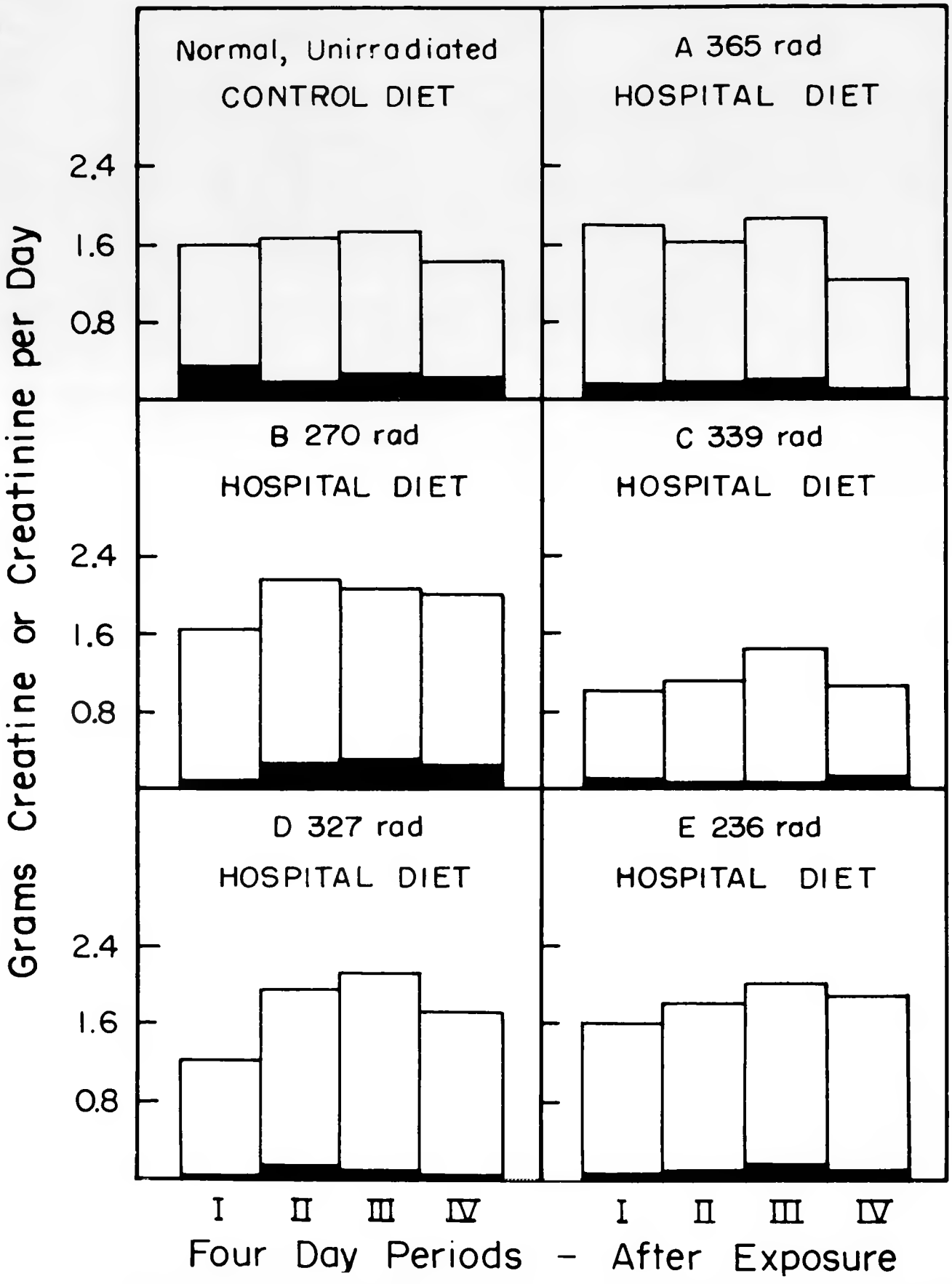

Figure 3. Creatine (solid rectangles) and creatinine (open rectangles) excretion by accidentally irradiated man. Data plotted in the same way as in Fig. 2.

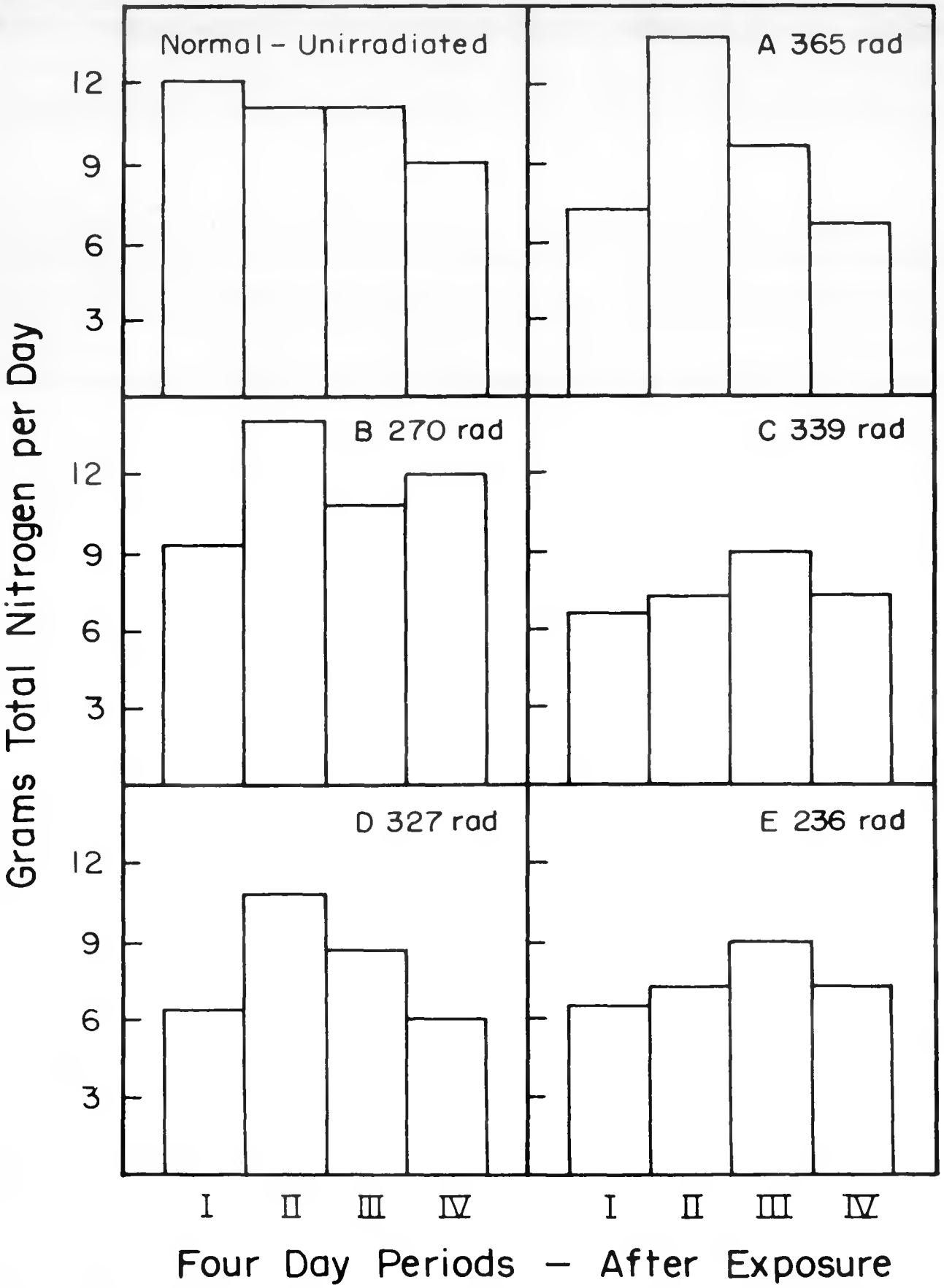

Figure 4. Total nitrogen excreted in the urine of five accidentally irradiated men. Data are plotted in the same way as in Fig. 2.

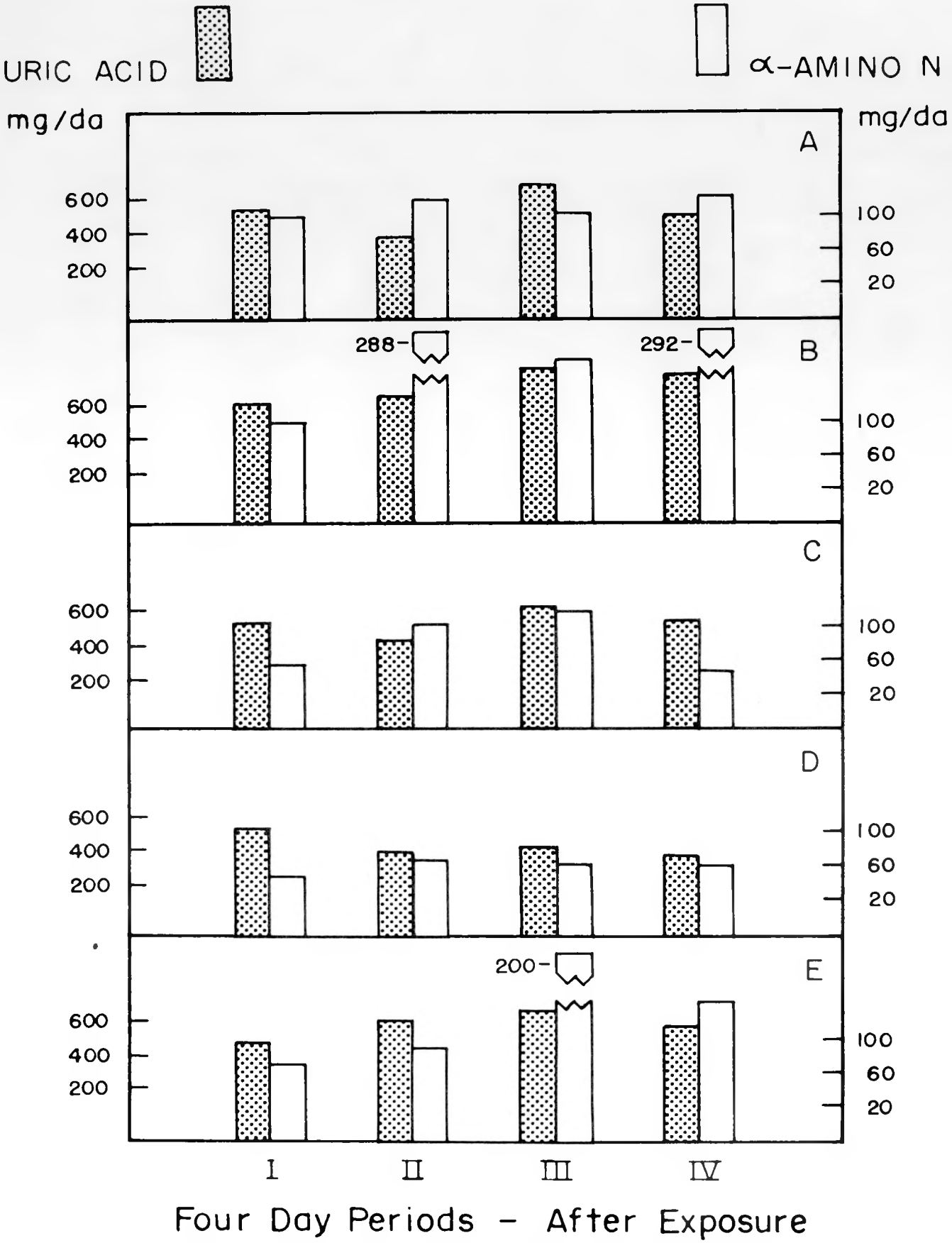

Figure 5. Uric acid and α-amino nitrogen in mg/day excreted in the urine of five accidentally irradiated men. The data are plotted as in Fig. 2.

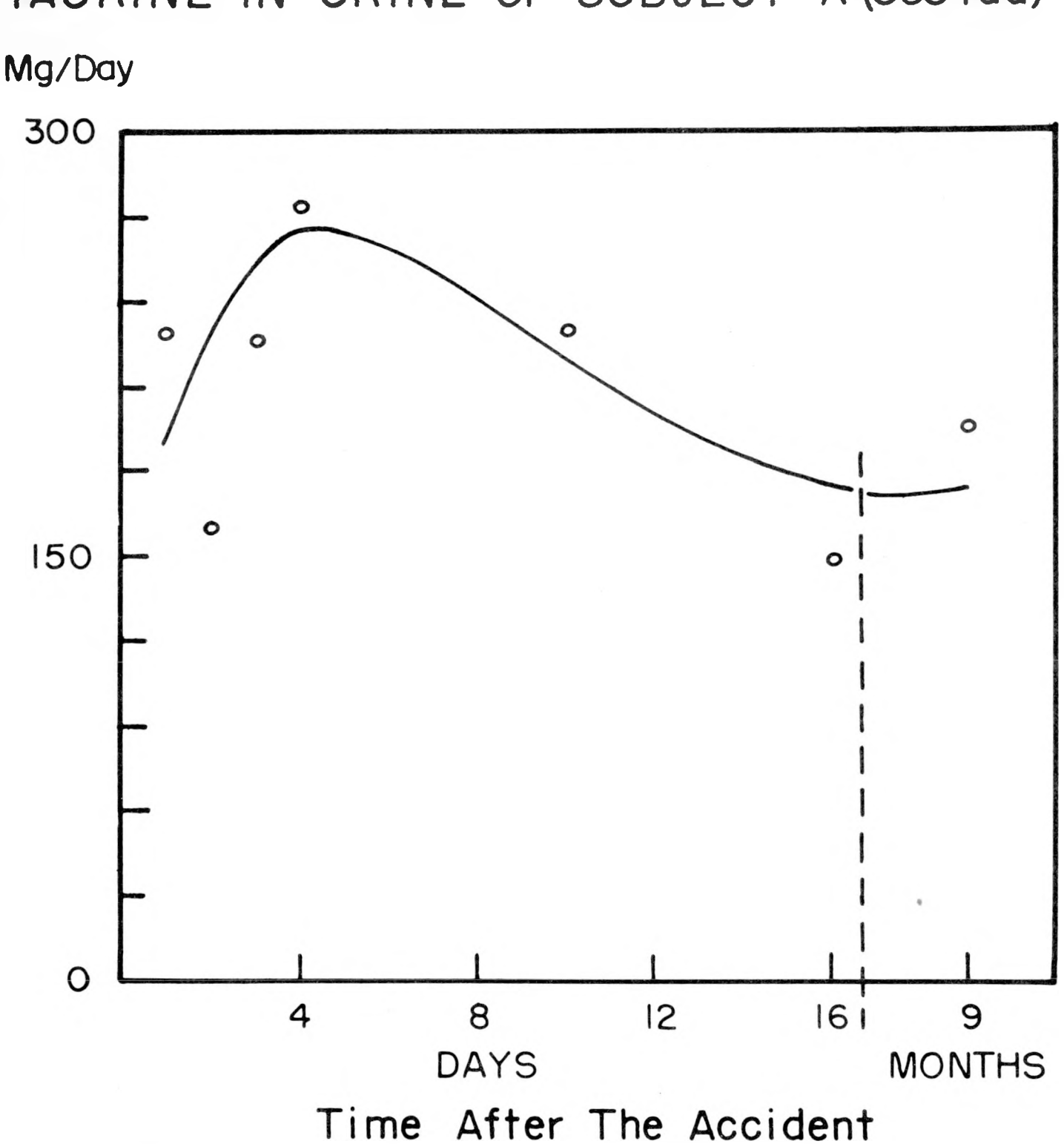

Figure 6. Changes in the excretion of taurine in the urine with time after accidental exposure of subject A to 365 rads of γ and neutron irradiation.

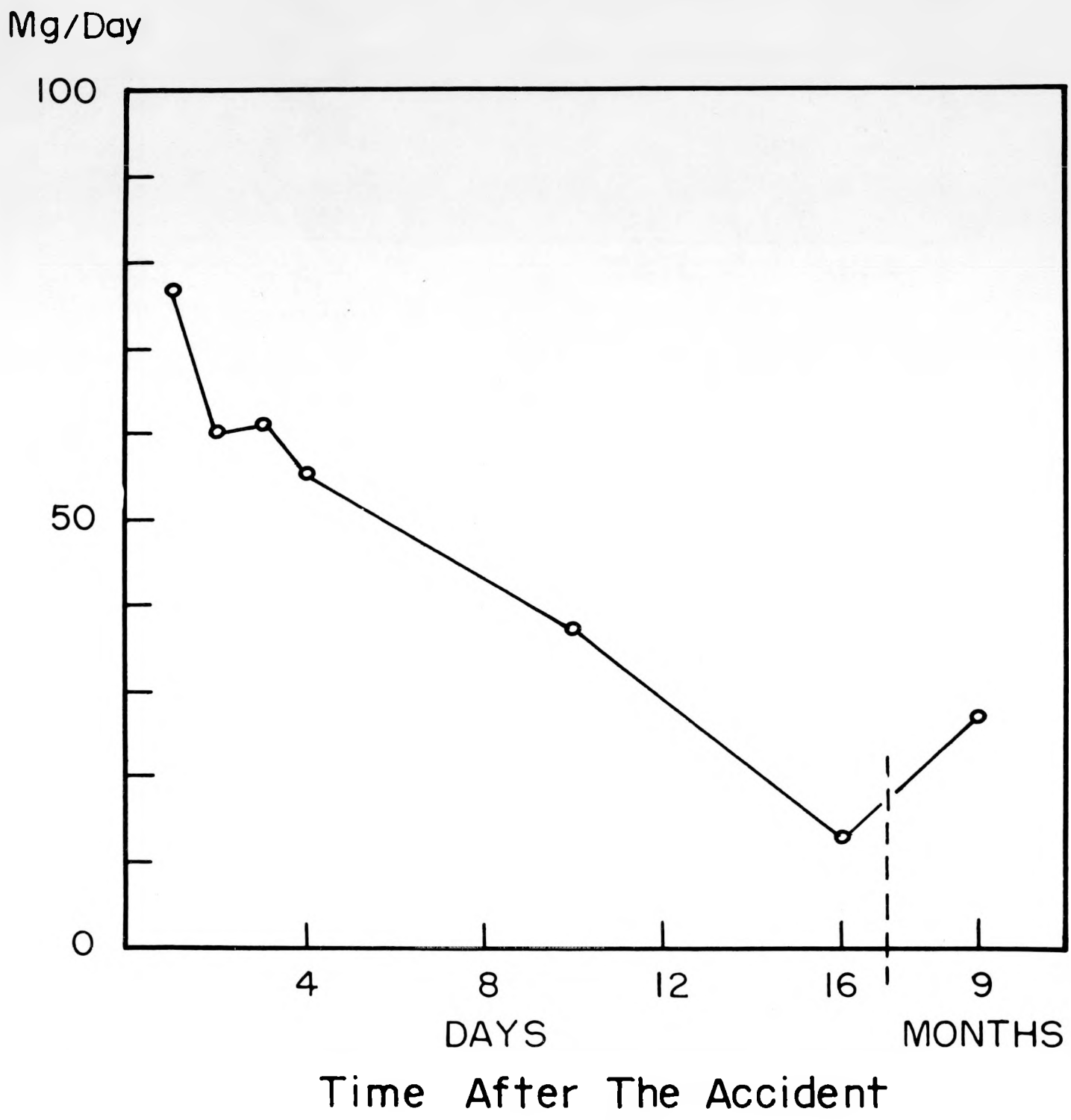

Figure 7. Changes in the excretion of beta-aminoisobutyric acid in the urine with time after accidental exposure of subject A to 365 rads of γ and neutron irradiation.

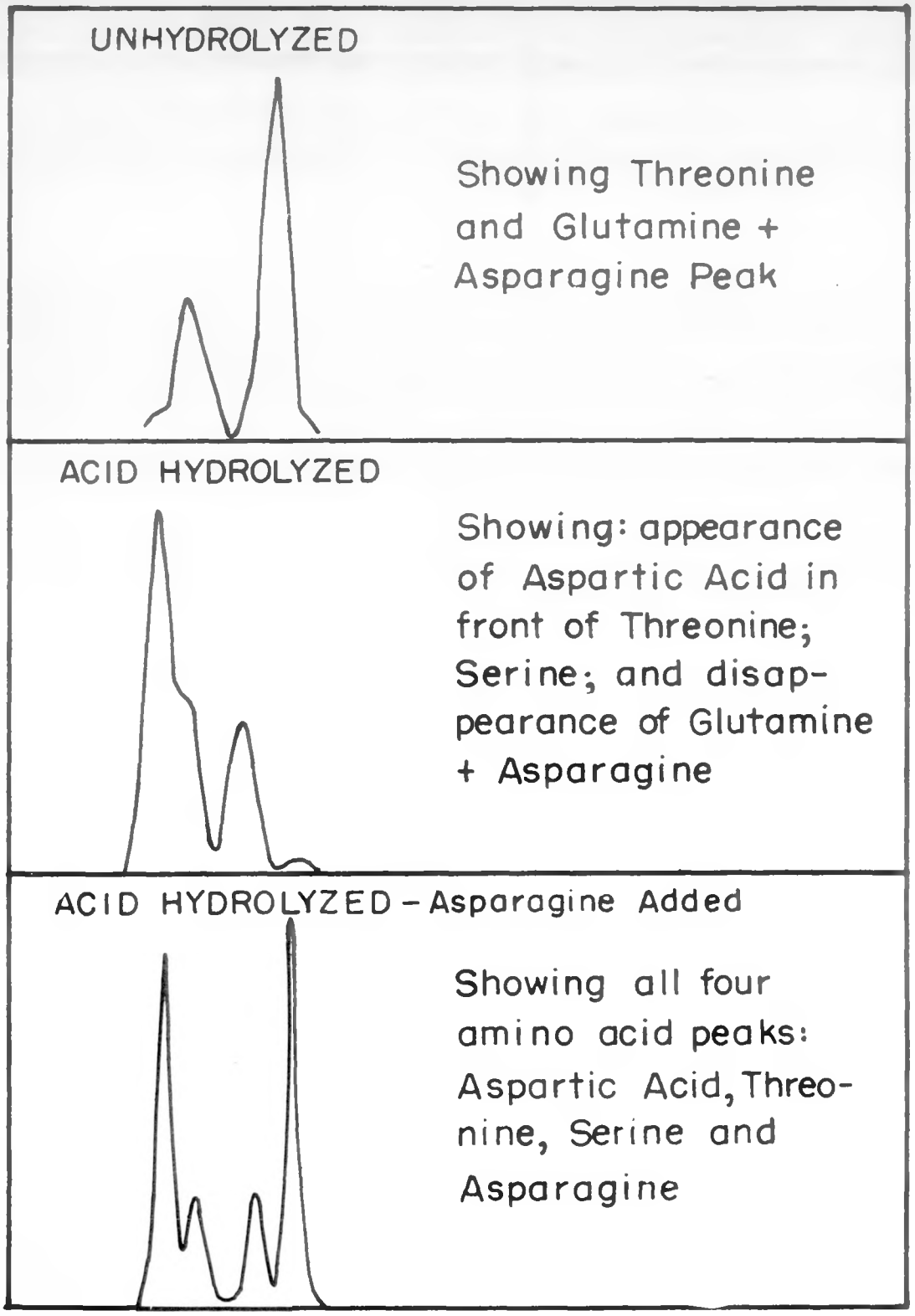

Figure 8. Artist's reconstruction from effluent diagrams taken from chromatographic studies of urine from subject A. In the unhydrolyzed urine there is no serine which should appear between the threonine and glutamine peak. In the hydrolyzed sample the glutamine + asparagine have been hydrolyzed to glutamic and aspartic acids. The hydrolysis has also liberated bound forms of serine so that a serine peak is seen in chromatograms of acid hydrolyzed urine. Asparagine was added back to urine after acid hydrolysis to show the position it assumes relative to serine.

The irradiated subjects excreted more beta-aminoisobutyric acid than normal persons usually excrete (Table 2). Patient A appears to have excreted the largest amount of this substance on the 1st day after exposure (Fig. 7). The levels decrease gradually during the first 10 days after exposure.

An extremely interesting observation is the absence of serine from the urine of these irradiated subjects (Fig. 8). The data are too preliminary to suggest possible reasons for this absence of serine.

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TABLE 1

Taurine in the Urine of
Accidentally Irradiated Humans

Subject and Interval after Exposure		Taurine Mg/Day
A (365)*	1st Day	228
	4th Day	273
C (339)	1st Day	204
E (236)	4th Day	231
F (68)	4th Day	109
I (0)**		103

* The numbers in parenthesis are the doses (γ + neutron) in rads.

** This was an ambulatory patient who had carcinoma of the lung but had not been irradiated.

TABLE 2

Beta Aminoisobutyric Acid in Urine
of Accidentally Irradiated Humans

Subject and Interval after Exposure		BAIBA Mg/Day*
A (365)	1st Day	77.4
	4th Day	54.8
C (339)	1st Day	38.4
E (236)	4th Day	15.7
F (68)	4th Day	13.6
I (0)		7.5

* To convert Mg/day to μM/day, multiply the numbers in this column by $\frac{1000}{103.1}$

URINE ANALYSIS REPORT

L. K. Akers, D. L. Coffey, H. K. Ezell, Jr., and E. Rona
(Special Training Division - ORINS)

The following is the neutron-exposure data compiled by Na^{24} assay and Na^{23} activation analysis of urine samples from five Y-12 employees who were patients at the ORINS Hospital

Patient	Na^{24} d/s ml (1)	Na^{23} mg/ml (2)	$\frac{Na^{24}\ d/s\ ml}{Na^{23}\ mg/ml}$	ft n/cm^2 (3) $\times 10^{10}$	rads (4)	rads (5) (correction for biological isotope dilution)
A	18.3	2.79	6.56	3.68	64	71.1
B	21.8	3.60	6.06	3.39	57	63.5
C	22.8	3.92	5.82	3.27	55	61.2
D	26.4	4.62	5.71	3.21	54	60.0
E	18.9	4.59	4.12	2.24	39	43.4

See next page for footnotes.

(1) Urine was received 11:00 a.m., June 18, 1958; correction was made for radioactive decay.

(2) Urine samples activated at ORNL.

(3) $ft = \frac{R\ T\ A}{0.693\ N\ W\ \sigma}$

f = flux

t = exposure time

R = d/s Na^{24}

T = $T\frac{1}{2}$ Na^{24}

A = atomic weight Na^{23}

N = Avogadro's number

W = weight of Na^{23}

σ = cross section

(4) Conversion factor of 1.75×10^{-9} rad/n/cm^2 was obtained from Mr. Ritchie of the ORNL Health Physics Division.

(5) The assumptions were made that Na^{23} intake and excretion per day were equal (4 g), that a total-body Na^{23} was 70 g, and that the Na^{24}/Na^{23} ratio was the same in blood as in urine. The Na^{24}/Na^{23} ratio after 42 hours represents approximately 90 per cent of the ratio at zero time.

Additional Urine Analysis:

A gamma-ray spectrum of urine samples showed a small amount of Cs^{137} in each sample.

Cesium-137 was found in patients' urine in the following concentrations ($\mu c/ml \times 10^{-5}$):

Patient A - 1.4
Patient B - 1.0
Patient C -<0.2
Patient D -<0.2
Patient E - 3.5

Beta spectrum of Patient A's urine showed beta maximum energies of 0.52, 1.52, and 2.12 Mev, which could possibly be Cs^{137}, Y^{91}, Y^{90} and Sr^{90}. One control on a nonirradiated person's urine gave negative results.

All data in this report were obtained from one urine sample (250 ml) from each patient.

THE URINARY EXCRETION OF BETA AMINOISOBUTYRIC ACID (BAIBA) IN IRRADIATED HUMAN BEINGS

J. R. Rubini*

Recently a previously unknown urinary amino acid, beta-aminoisobutyric acid (BAIBA) has been identified in human urines by Crumpler, Dent, et al. (1), and Fink, et al. (2). Further studies by Fink using labeled thymine indicate that BAIBA is a product of thymine metabolism (3,4) as shown in Fig. 1. Since thymine is a pyrimidine peculiar to deoxyribonucleic acid (DNA), it appears likely that under certain circumstances BAIBA excretion may reflect DNA metabolism.

In June, 1958, there occurred at Oak Ridge an accidental fission reaction in which five persons were exposed to large doses of total-body irradiation while three others received lesser amounts. In the course of their subsequent stay in the hospital for treatment and study, serial 24-hour urine volumes were obtained and aliquots were used for measurement of BAIBA excretion. The preliminary results shown here indicate that significant increases of BAIBA excretion occur after serious radiation exposure and suggest that BAIBA excretion may be helpful in indicating the extent of radiation damage.

Materials and Methods

Frozen 24-hour urine aliquots were thawed and processed for BAIBA measurement by means of the method described by Awapara and Sato (6), with certain modifications.

Ten milliliter aliquots of the urines were mixed with 1-gram portions Darco G-60 charcoal and heated briefly in a water bath. After centrifugation, 6.0 ml of the charcoal-treated urines were placed on Dowex-2 columns (previously converted to the hydroxide form) for desalting. After the urine supernatants had entered the resin beds,

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THYMINE METABOLISM

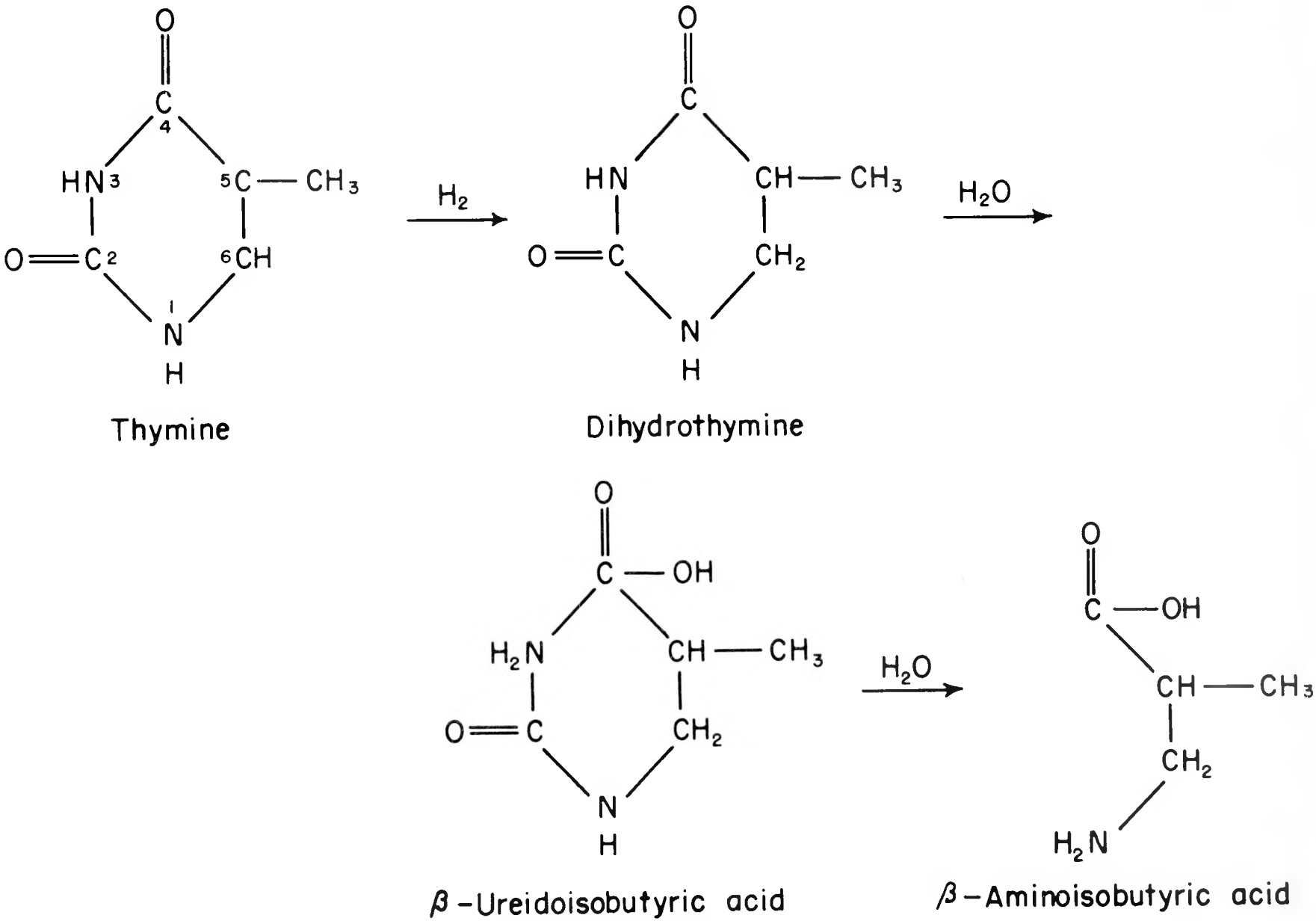

Figure 1

the columns were washed with cold, boiled distilled water until the effluent became neutral. Elution with enough 4N acetic acid to collect 10 ml of eluate followed. The eluates were lyophilized and the resultant dried materials were dissolved in 1 ml portions of distilled water. These concentrates were frozen until ready for chromatography.

Two-dimensional chromatography was used in identifying BAIBA. Ten lambda (0.01 ml) of the concentrates were each spotted on 8-inch squares of Whatman No. 4 paper held in the frame described by Datta, et al. (7), which holds 12 papers at a time. Solvent 1 was butanol, acetic acid, water (5:1:4); solvent 2 was 2,4-lutidine saturated with water. After drying, the papers were sprayed with ninhydrin reagent and the color was developed by heating at 100° C.

Known amounts of BAIBA of varying concentrations were made up similarly in water and chromatographed. Beta aminoisobutyric acid was readily identified by Rf measurement (RF 1 = 0.45 ± 0.02; Rf 2 = 0.32 ± 0.02) and the intensity of the spots was graded 0 to +++++ by two independent observers. Estimation of BAIBA in urines in micromoles per liter was performed by comparison with standards and calculated on the basis of 24-hour urine volume. Duplicate determinations gave reasonably reproducible agreement.

It should be noted that adding known amounts of BAIBA to normal urines, which previously showed no BAIBA by this method, resulted in ninhydrin spots of significantly less intensity compared with water solutions of BAIBA of equal concentration similarly processed. It appears that the results of urine BAIBA determinations shown here are less than quantitative because of possible loss of some BAIBA passing through the column with the urine electrolytes. Experiments to further investigate this problem are now under way.

Results

Table 1 shows the measured daily urine BAIBA levels of the eight men admitted to the ORINS hospital after radiation exposure. Urine collections from the 3rd to 8th day were used in this study. An estimate of the radiation dose that was available shortly after the accident is shown as well as the final estimate. Independent of urine volume (assuming all excreted exactly a liter of urine each day), it is seen that BAIBA excretion is distinctly increased in these irradiated human beings. If one can accept the physical dose estimation, it appears that there may be dose dependency of BAIBA excretion after irradiation.

When 24-hour urine volumes (to the nearest 100 ml) were taken into account for the more seriously exposed patients, further fluctuations of BAIBA became apparent, as shown in Fig. 2. It is seen that after an initial elevation of BAIBA excretion there is a decrease followed perhaps by a secondary rise.

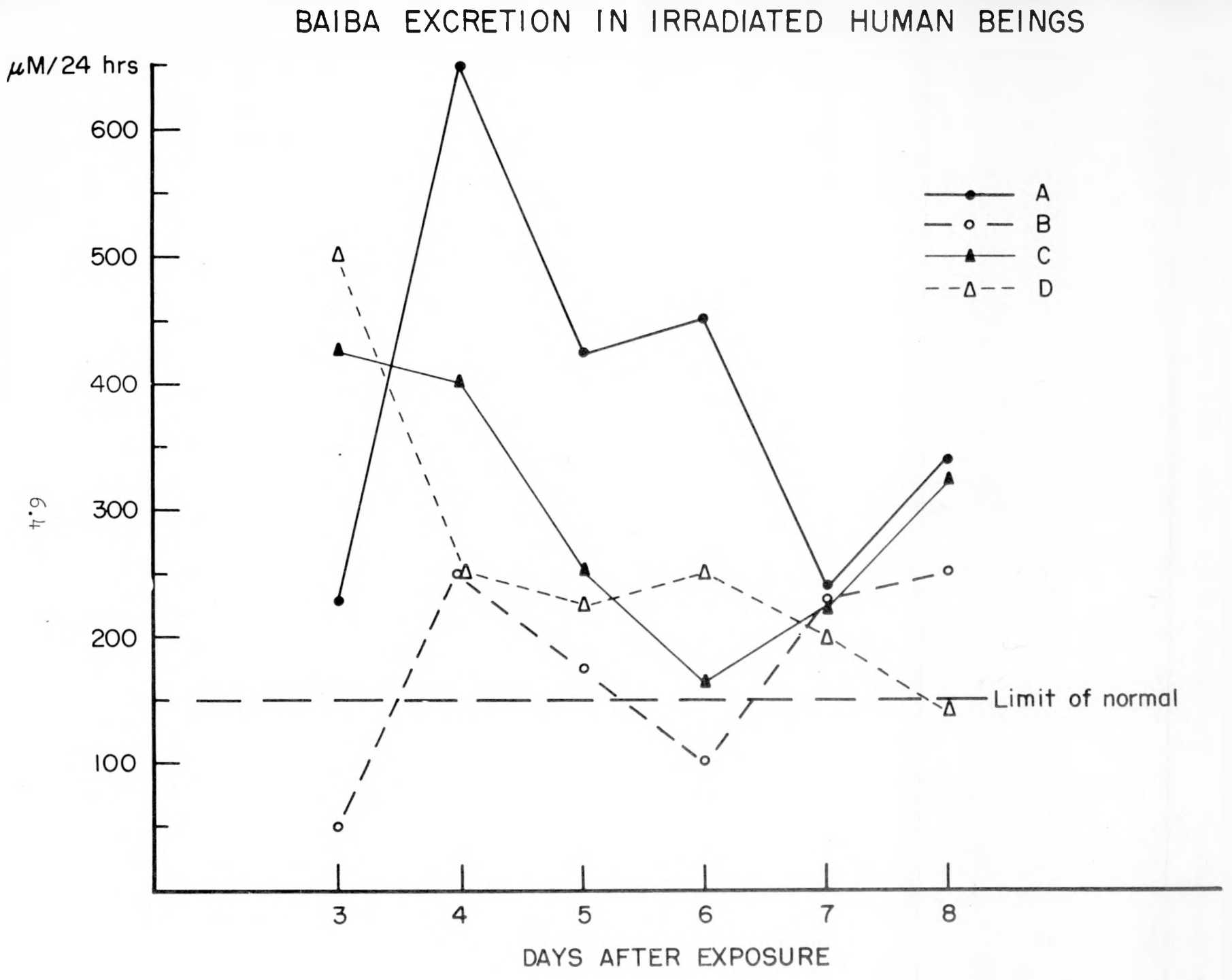
BAIBA EXCRETION IN IRRADIATED HUMAN BEINGS
μM/24 hrs
600
500
400
300
200
100
A
B
C
D
Limit of normal
3
4
5
6
7
8
DAYS AFTER EXPOSURE

Figure 2

Discussion

That BAIBA excretion is increased during the first week following radiation exposure is evident from these preliminary data in Table 1 and Fig. 2. These levels of BAIBA excretion shown are significantly above normal by our method. Fink, et al. reported that of a large series of apparently normal human beings, 60 per cent excreted less than 150 μM/L while most of the rest excreted BAIBA at about this level with her method (8). Awapara (9), reviewing Fink's data on normals, concluded that detectable BAIBA excretion was "an uncommon event." Although their techniques are somewhat different from those described here, we have found no detectable BAIBA in four urines of two apparently normal persons and usually none to <150 μM/L in urines from a variety of inpatients who did not have neoplastic diseases (unpublished data). Also from Table 1 it is seen that the Oak Ridge patients not believed to have received serious exposure excreted only small amounts of BAIBA. We are currently studying the effect of graded doses of X ray on a group of dogs, and early results have again shown that BAIBA excretions were markedly increased in two dogs as early as 18 hours after irradiation, 400 r total-body, while no BAIBA was detected in a control-animal urines.

Radiation damages living tissue. The increase of BAIBA excretion following exposure suggests that BAIBA determination of urine may be used as an indication of serious radiation damage, by reflecting DNA catabolism. Furthermore, if quantitation of BAIBA excretion relating to DNA catabolism can be achieved, it may be possible to estimate the amount of DNA catabolized and, therefore, achieve an estimate of the number of cells destroyed. It must be recognized, however, from the data of Fink, et al., that BAIBA is only one of a number of possible products appearing from thymine metabolism. Indeed, studies by Carvaca and Grisolia (10) and others, indicate that BAIBA may arise in part from sources other than thymine, such as carbamyl amino acids. Despite these limitations, it appears likely that marked cell destruction with resultant DNA catabolism will be associated with increased BAIBA excretion. This type of information might be used in detecting early rejection of bone-marrow transplants, in aplastic states, which cannot be detected by present methods until a number of days later (11). Efforts along these lines are under way.

Summary

1. Beta-aminoisobutyric acid (BAIBA), a newly discovered urinary amino acid, has been found in urines from a group of human beings accidentally exposed to serious radiation.

2. Levels of BAIBA excreted appear related to the estimated doses received.

3. The implications of BAIBA excretion as related to DNA metabolism are discussed.

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3. Fink, K., Henderson, R.B., and Fink, R.M. β-aminoisobutyric acid in rat urine following administration of pyrimidines. J. Biol. Chem. 197, 441-452, 1952.

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5. Unpublished data.

6. Awapara J. and Sato, Y. Paper chromatography of urinary amino acids. Clin. Chim. Acta 1, 75-79, 1956.

7. Datta, S.P., Dent, C.E., and Harris, H. Apparatus for mass-production two-way paper chromatography. Biochem. J. 46, Proceedings Section, p. 42, 1950.

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9. Awapara, J. Urinary amino acid excretion in leukemia. In "The Leukemias: Etiology, Pathophysiology, and Treatment; Henry Ford Hospital International Symposium." New York, Academic Press, 1957, Chapter 20, pp. 353-360.

10. Caravaca, J. and Grisolia, S. Enzymatic decarbomylation of carbamyl β-alanine and carbamyl β-aminoisobutyric acid. J. Biol. Chem. 231, 357-365, 1958.

11. Transplantation of Bone Marrow I. Blood Club Meeting, Atlantic City, New Jersey, May 5, 1957. Blood 13, 266-288, 1958.

Table 1

Urine BAIBA Excretion Following Radiation Exposure
Based on 10 ml Aliquots (Independent of 24-hour Volume)

Patient	A	B	C	D	E	F	G	H
Early Estimated Exposure in rads								
Neutrons	66	45	55	57	39	14	8	4
Gamma	210	143	175	182	114	43	34	17
Total	276	188	230	239	153	57	42	21
Finally Estimated Exposure in rads	365	270	339	327	236	68.5	68.5	22.8
Day 3	++	0	+	++	±	+	0	0
4	+++	+	++	++	+	0	0	0
5	++	±	+	+	±			
6	++	±	+	+	0			
7	+	±	+	+	±			
8	+	±	+	±	±			

0 = 50 µM/L BAIBA
± = 75 µM/L BAIBA
\+ = 125 µM/L BAIBA
++ = 250 µM/L BAIBA
+++ = 500 µM/L BAIBA

SERUM PROTEIN STUDIES

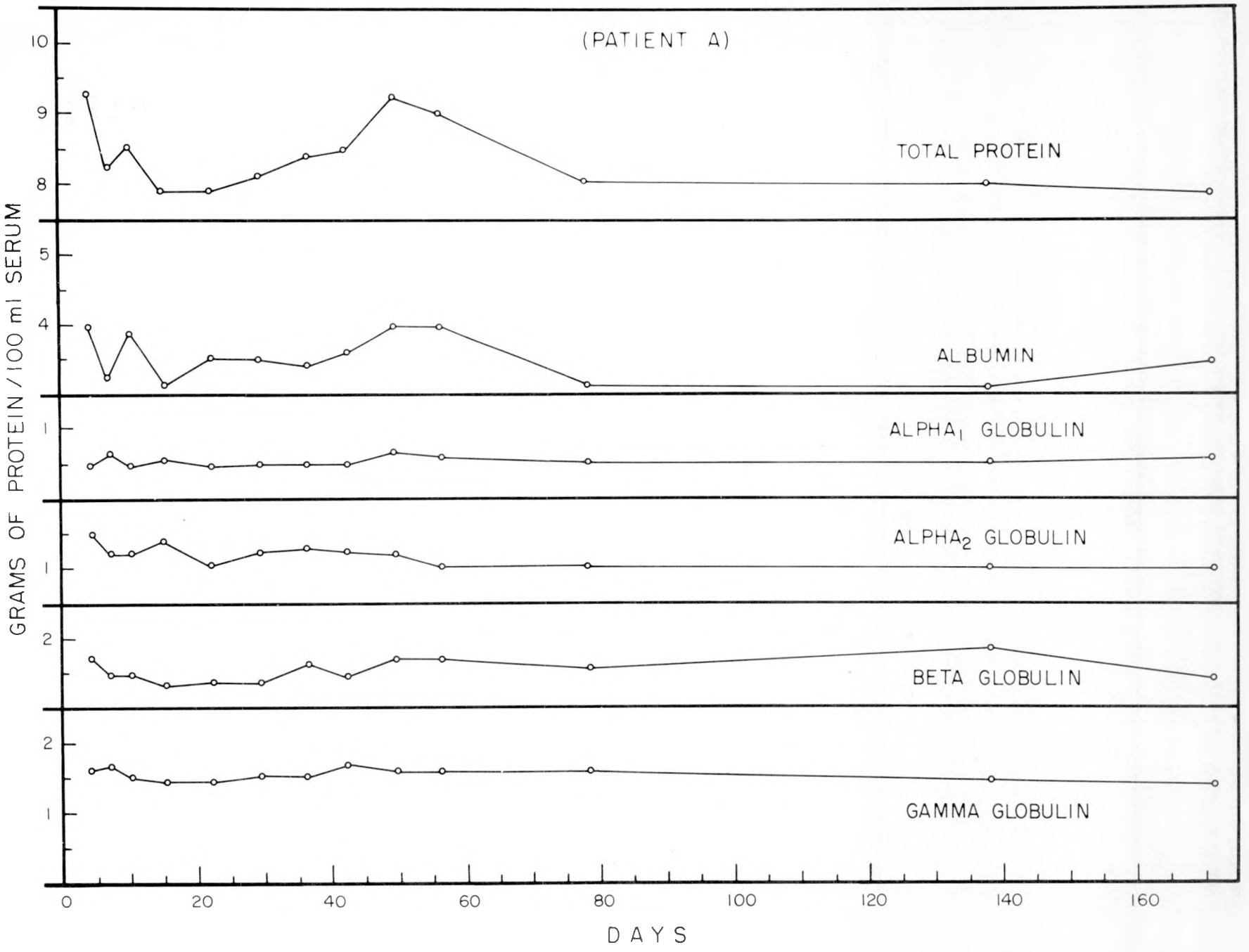
Granvil C. Kyker
with the technical assistance of
Lois A. Gerst

The total protein and serum protein fractions of eight patients that received accidental total-body irradiation were measured at intervals over about six months. The specimens were taken 4, 7, 10, 15, 22, 29, 36, 42, 49, 56, 78, 138, and 172 days after the accident. The eight patients were divided into two groups: five (A through E) were estimated to have received a higher exposure to neutron and gamma irradiation than the other three (F, G, and H). (See Clinical Report for estimated dose, symptoms, and treatment.)

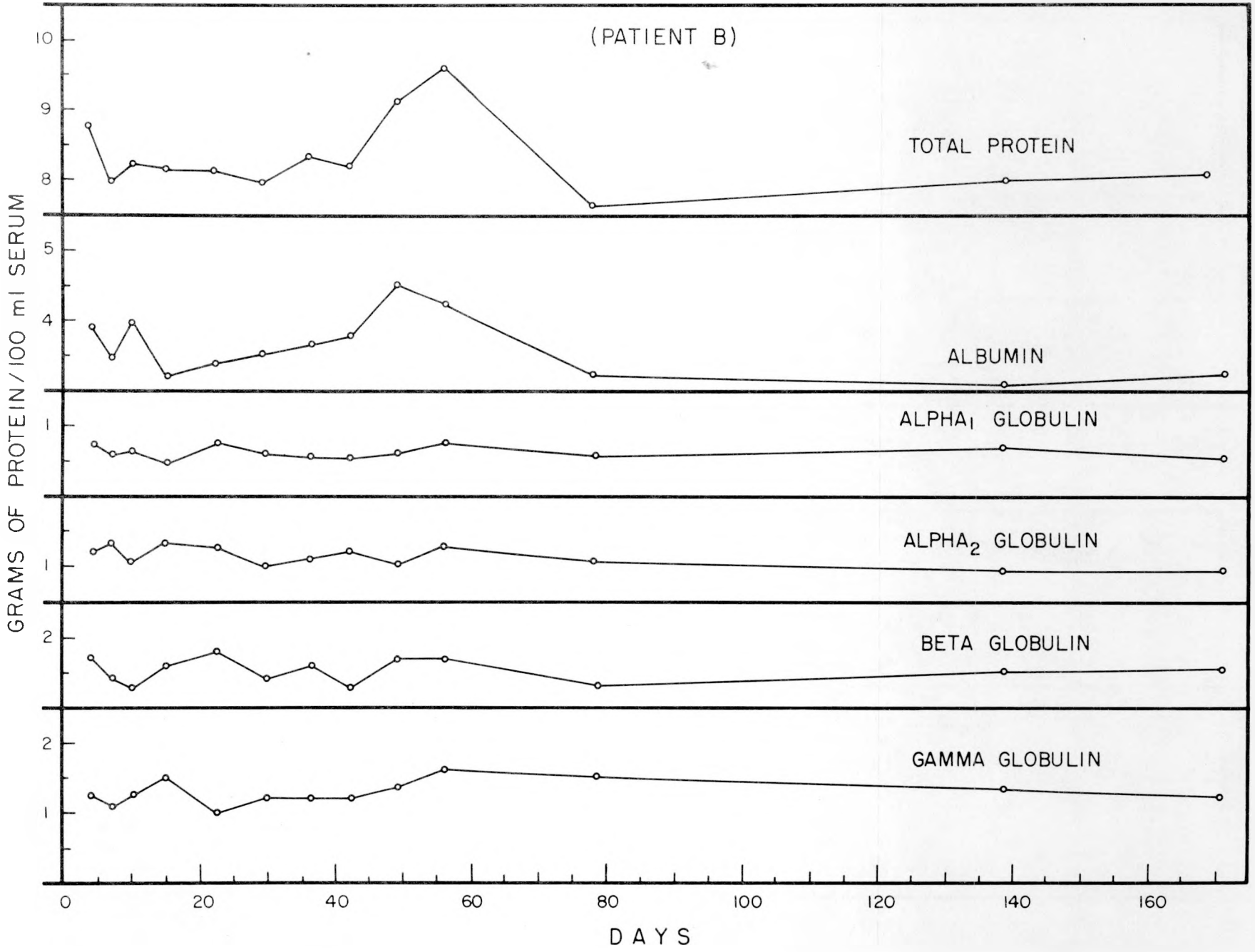
Total serum nitrogen was measured by the Kjeldahl method and the total serum protein was calculated. Five fractions of protein (albumin, $alpha_1$-, $alpha_2$-, beta-, and gamma-globulin) were estimated by paper electrophoresis. In the eight charts, the levels of total protein and of the five fractions are plotted against days after irradiation.

Distinct changes occurred in the total protein levels of each of the first group of patients (A through E). The first specimen from each patient (on the fourth day) indicated hyperproteinemia. Normal levels of protein were regained during the second week and persisted from two to three weeks, after which each of the five developed a recurring hyperproteinemia during the next three to four weeks. This peak recurred during the eighth week in each patient; the protein level returned to normal within another three weeks, and remained so throughout the rest of the study.

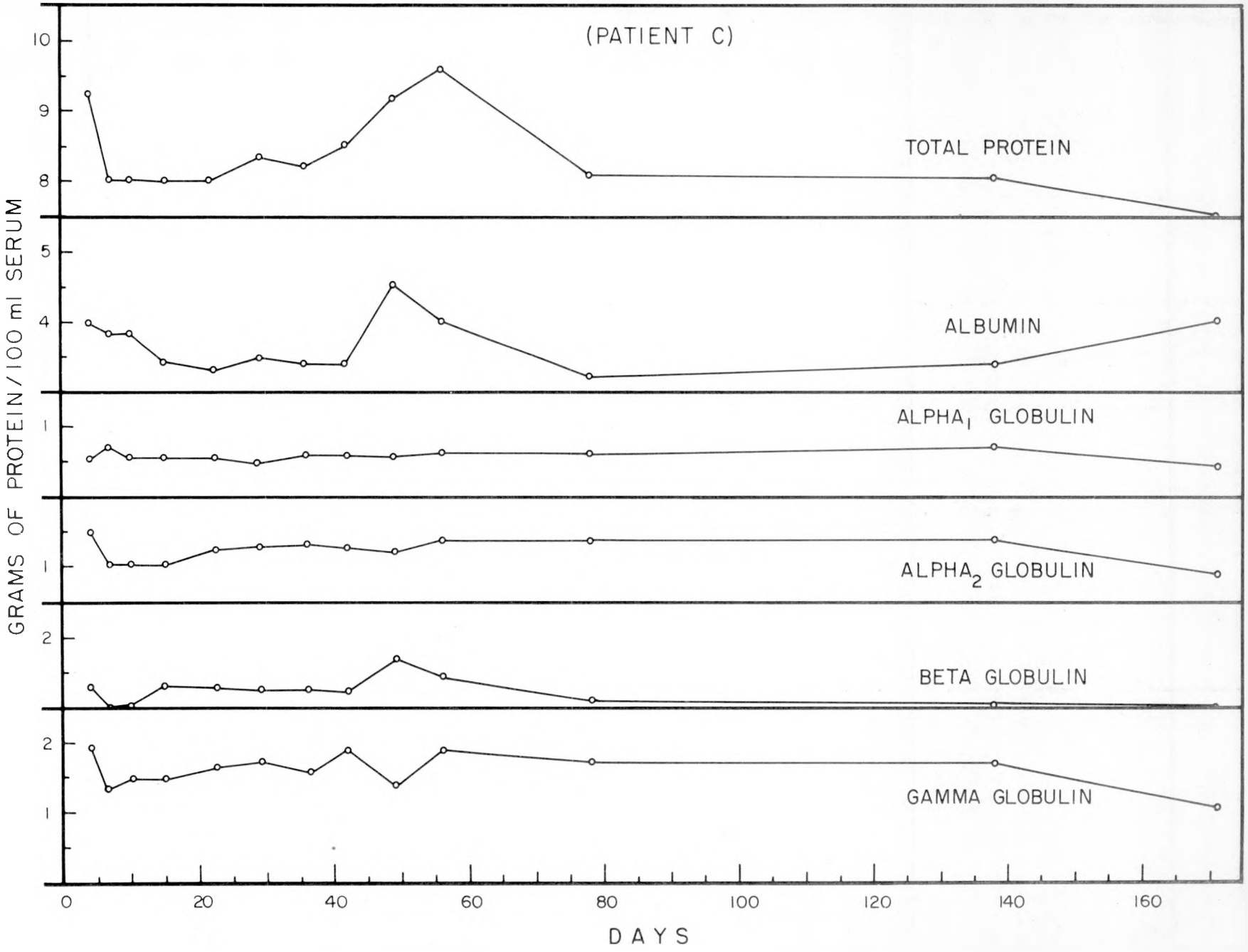
The changes described for total protein levels were mainly accounted for by the albumin fraction. The globulin fractions showed no consistent pattern of changes. The level of $alpha_1$-globulin remained essentially the same throughout the period of six months. The $alpha_2$- and beta-globulin fractions showed more variation among specimens from the same patient and among patients but yielded no consistent pattern of behavior. Gamma globulins appeared somewhat elevated and showed a tendency to decrease slightly during the second three months.

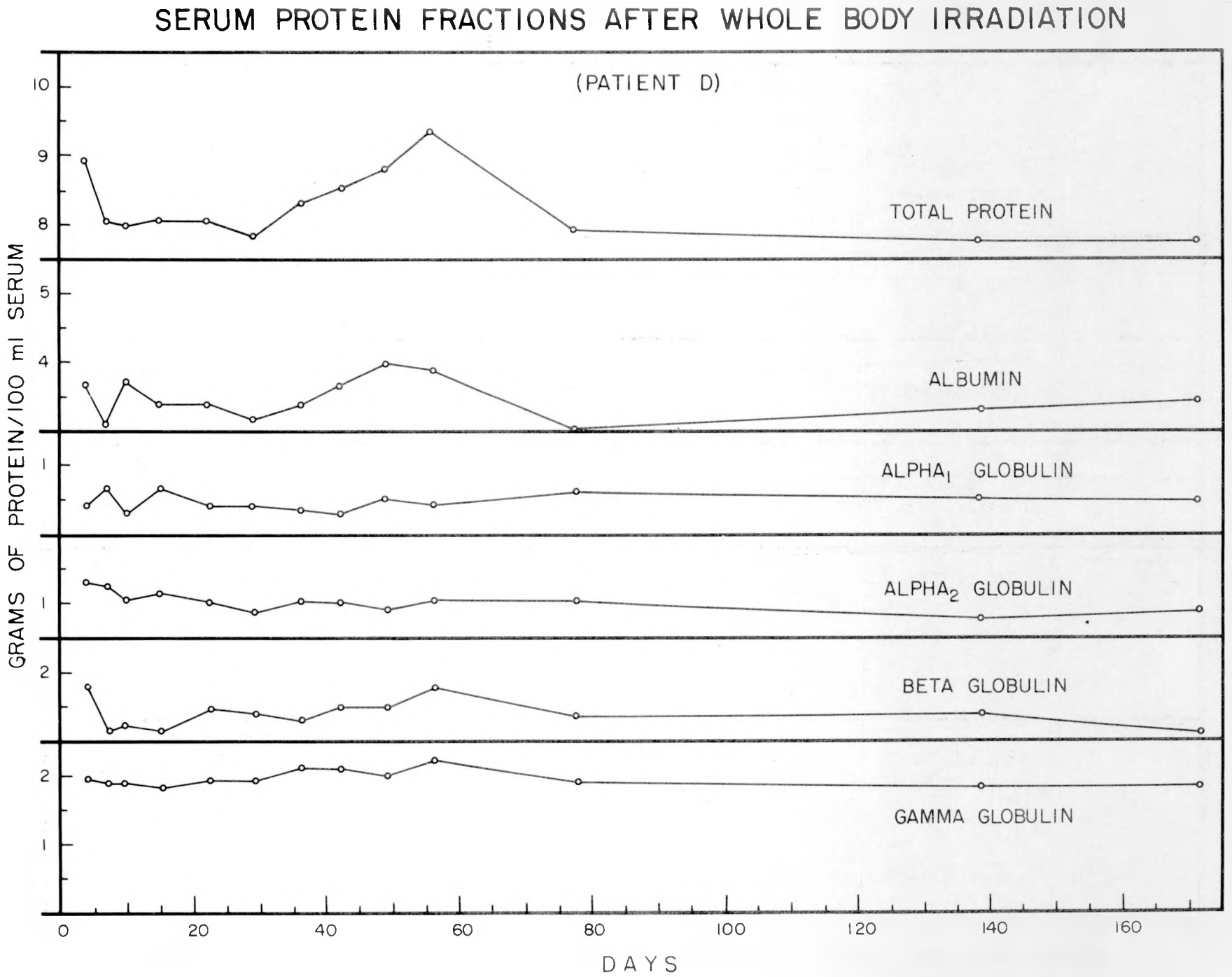

SERUM PROTEIN FRACTIONS AFTER WHOLE BODY IRRADIATION
(PATIENT A)
TOTAL PROTEIN
ALBUMIN
ALPHA1 GLOBULIN
ALPHA2 GLOBULIN
BETA GLOBULIN
GAMMA GLOBULIN
GRAMS OF PROTEIN / 100 ml SERUM
DAYS
10
9
8
5
4
1
1
2
2
1
0
20
40
60
80
100
120
140
160

SERUM PROTEIN FRACTIONS AFTER WHOLE BODY IRRADIATION

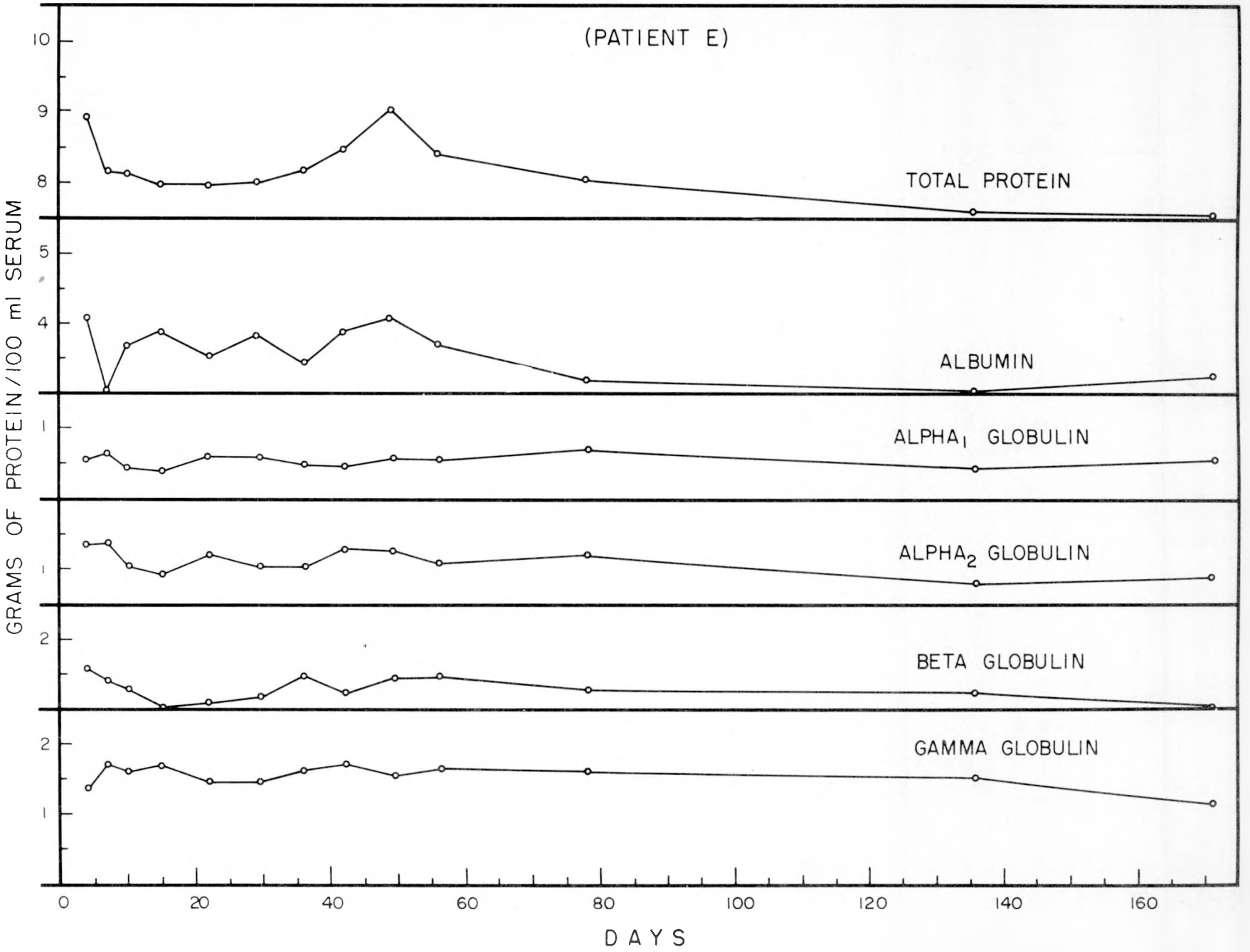


SERUM PROTEIN FRACTIONS AFTER WHOLE BODY IRRADIATION




SERUM PROTEIN FRACTIONS AFTER WHOLE BODY IRRADIATION
(PATIENT D)
TOTAL PROTEIN
ALBUMIN
ALPHA1 GLOBULIN
ALPHA2 GLOBULIN
BETA GLOBULIN
GAMMA GLOBULIN
GRAMS OF PROTEIN/100 ml SERUM
DAYS
0
20
40
60
80
100
120
140
160

SERUM PROTEIN FRACTIONS AFTER WHOLE BODY IRRADIATION



The three patients (F, G, and H) that received less total-body irradiation showed the initial hyperproteinemia, regained a normal protein level within one or two weeks, and showed no tendency toward the recurring elevated levels during the second month. In general the characteristics of a lack of any consistent pattern in alpha$_1$-, alpha$_2$- and beta-globulin and a slight gradual decrease of gamma-globulin that were described for the first five patients also applied.

The protein fractions of three sera (on the 22nd, 29th, and 36th days) from the five patients of the first group (A through E) were studied also by starch-gel analysis. These were appraised to show no gross abnormalities (1).

Related experimental studies (2) on the effect of total-body irradiation on serum proteins deal largely with X irradiation of small experimental animals with relatively large doses. The various dose-dependent effects that have been mentioned include decreased albumin/globulin ratios, increased alpha and beta globulins, and a decreased gamma-globulin level. The present observations on human patients include part of these effects to a mild extent. Extrapolation from one set of conditions to the other is not possible and any present correlation is empirical.

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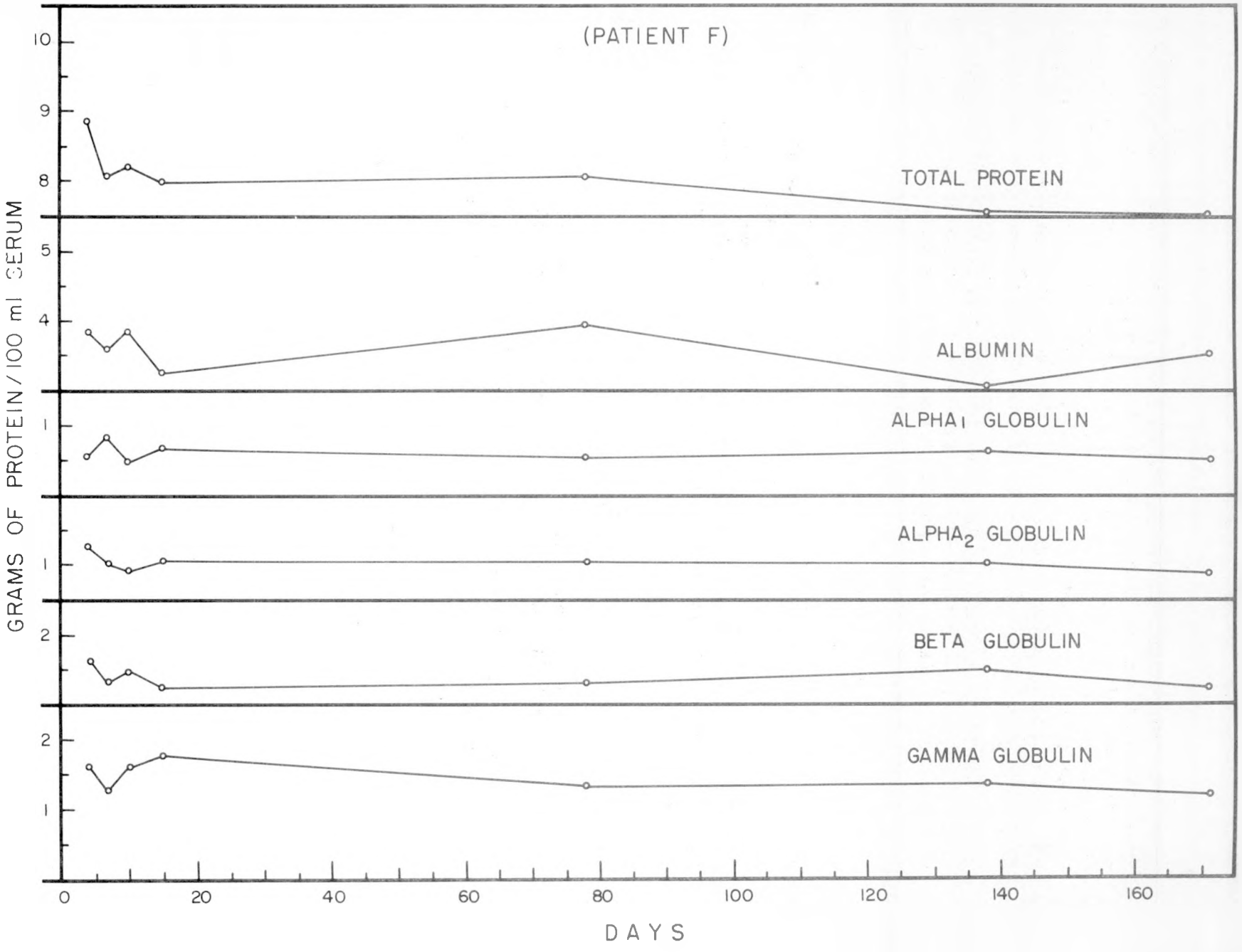
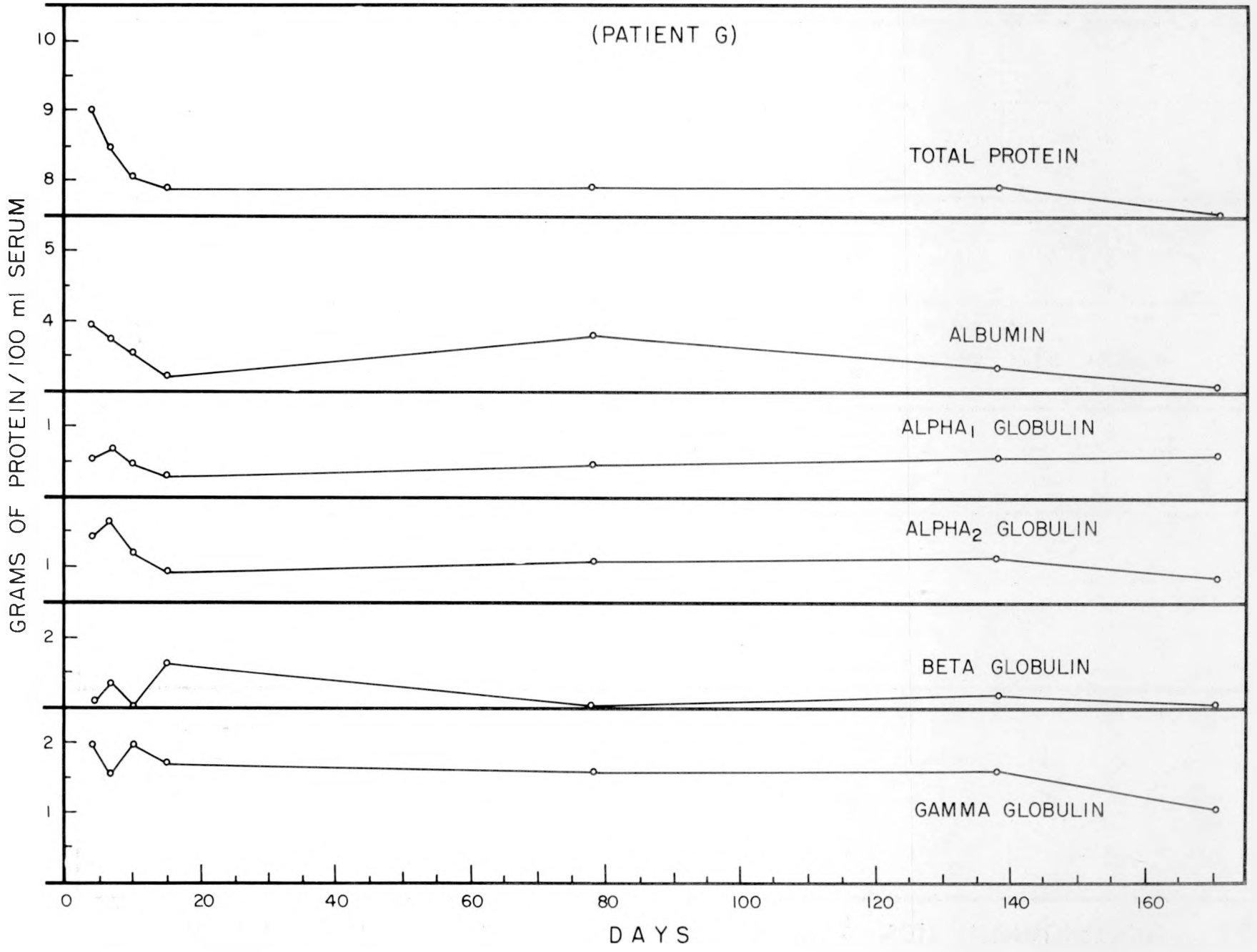
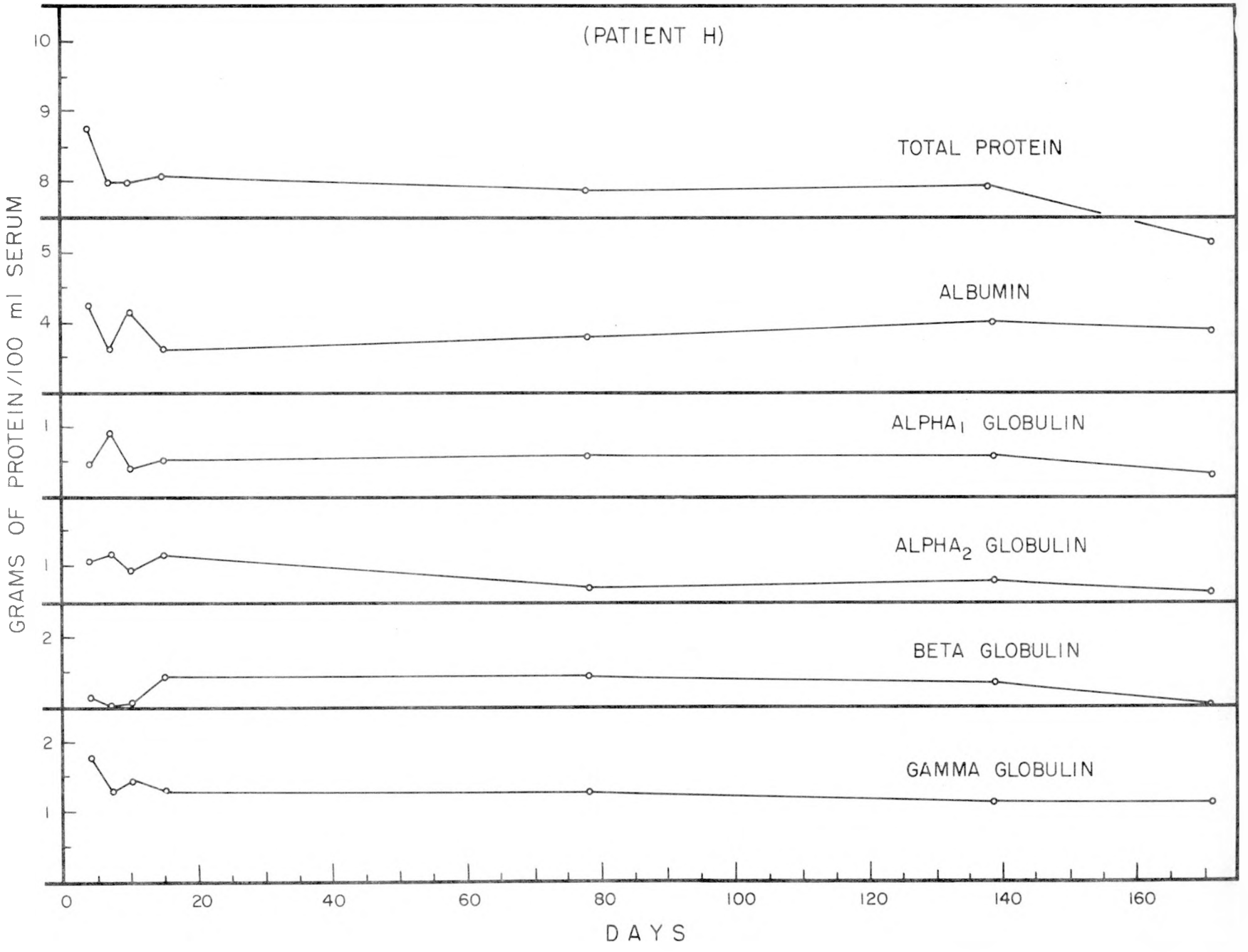

SERUM PROTEIN FRACTIONS AFTER WHOLE BODY IRRADIATION
(PATIENT F)
GRAMS OF PROTEIN / 100 ml SERUM
TOTAL PROTEIN
ALBUMIN
ALPHA1 GLOBULIN
ALPHA2 GLOBULIN
BETA GLOBULIN
GAMMA GLOBULIN
10
9
8
5
4
2
2
1
0
20
40
60
80
100
120
140
160
DAYS

SERUM PROTEIN FRACTIONS AFTER WHOLE BODY IRRADIATION



SERUM PROTEIN FRACTIONS AFTER WHOLE BODY IRRADIATION



BACTERICIDAL POWER OF HUMAN SERUM AFTER MASSIVE IRRADIATION

David Jacobson, Abraham Braude, and Niel Wald*

The bacteremia of enteric origin in animals subjected to lethal irradiation suggests that intestinal Gram-negative bacilli might establish fatal bacteremia in massively irradiated persons. Sera obtained from eight persons involved in a recent atomic accident were therefore examined for bactericidal power in order to evaluate their resistance to systemic attack by intestinal pathogens. Five subjects had been exposed to 236 to 365 rads and sustained severe leukopenia; two others received 68.5 rads and one, 22.8 rads without hematologic disturbances. All survived.

Bactericidal activity at 37° C was measured by inoculating 5,000 to 10,000 viable cells of Escherichia coli into each milliliter of serum and performing serial plate counts. The sera were obtained at weekly intervals for one month after the accident through the Medical Division, Oak Ridge Institute of Nuclear Studies, and stored at -15° C. After thawing at 4° C for 18 hours, all sera were examined simultaneously for bactericidal activity.

Unheated sera of all irradiated subjects were as strongly bactericidal as normal serum and usually sterilized the inoculum within 24 hours. Heated sera (56° C for 30 min) also became sterile, or nearly sterile, by 24 hours; but their bactericidal rate during the first four hours was reduced 50 per cent through loss of complement.

These results demonstrate that bactericidal power of serum against enteric Gram-negative bacilli is not reduced by exposure to massive irradiation, and that both complement-dependent and complement-independent bactericidal systems remain intact. From these data, therefore, we believe that bacteremia by enteric Gram-negative bacilli may not contribute seriously to the morbidity or mortality of massive human irradiation.

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LINEAR SCANS

D. A. Ross

Within a day after the Y-12 accident, linear scans had been run on each of the five most heavily irradiated patients, and the scans were repeated at roughly one-day intervals until the activity was no longer demonstrable. The five series of scans are found at the end of this section.

Ideally, a linear scan is a plot of the radioactivity contained in successive, thin, cross sections of a patient's body as one passes from head to foot. It therefore shows the distribution of the activity along the longitudinal axis, leaving lateralization and dorsoventral localization to later studies. In the ORINS redesign of the original "profile scanner"* the patient lies on his back on a horizontal carriage, which rolls on tracks so that the whole of the patient is passed longitudinally through the detecting area. The single Geiger tube of the earlier design has been replaced by a system of scintillation crystals (sodium iodide, 2" x 2"), which provides much better efficiency. Constancy of lateral sensitivity is encouraged by setting up six of these crystals in a transverse row above the patient, and pooling their outputs. Furthermore, the dorsoventral nonuniformity found in earlier designs has been greatly reduced by providing a duplicate row of crystals located under the patient and looking upward. The heights of the upper and lower detecting heads are adjustable, so that the center of the patient can be placed midway between the two sets of crystals. The illustration shows the arrangement of the traveling support, the patient, and the two detecting heads. A variable-speed motor drives the carriage and patient slowly between the detectors at constant speed, and while

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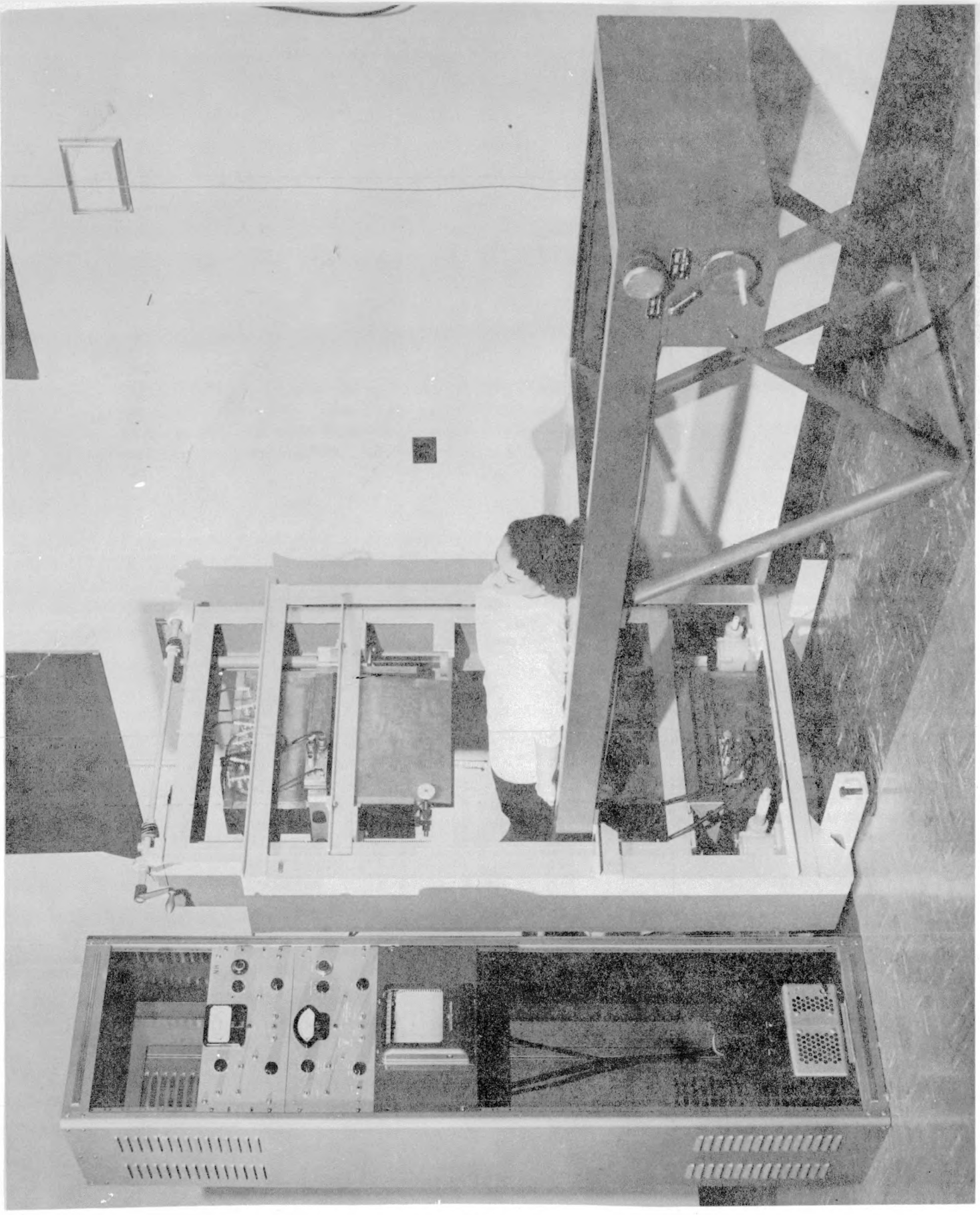
* Corbett, B.D., Cunningham, R.M., Halnan, K.E. and Pochin, E.E. A profile counter and its calibration. Physics in Biology & Medicine 1, 37-56, 1956. The ORINS version was developed largely through the work of Mr. A. C. Morris, Jr. of the Medical Division, and it is still undergoing modifications and improvements. For the series of scans under discussion, the machine was operated by Dr. Akira Tsuya and Mr. Kandiah Shivanandan



this is being done the count rate is recorded continuously by a direct-writing galvanometer. The sensitivity of the detectors in the longitudinal direction is cut off abruptly by thick lead jaws between which the crystals can see only a relatively thin slice of the patient. The slit between the collimating slabs is adjustable to suit the individual situation, and is routinely made the same for the upper and lower heads.

With such an instrument the experimenter can find out not only what the longitudinal distribution of the activity is, but he can also obtain some idea of the total activity present in the patient, by considering the area lying under each linear scan. Thus successive scans can show the decay - biological or physical - of the radioactivity in a patient, as well as any longitudinal shifts of position that might occur.

At the time of the Y-12 accident the linear scanner had just been built, and its calibration was only in its very early stages. We therefore have no more than an order-of-magnitude idea of the total activities involved. Our best guess, currently, is that in the 24-hour scans the total activities in these patients were something of the order of 10 microcuries, the chief active element presumably being sodium-24, produced through neutron bombardment of the naturally occurring sodium-23. The radioactive form has a half life of 15 hours, and although its rate of disappearance from these patients, as shown by the linear scans, does not permit a good estimate of the half life (because excretion and other biological effects complicate the picture) nevertheless the fall-off of the activity seems wholly consistent with the supposition that the main element concerned was sodium-24. The scanner is provided with a pulse-height analyzer, but spectral identification of the emitter(s) was not possible with the low count rates available; in order to obtain workable profiles the operators were forced to utilize all the counts they could get their hands on, and to this end the energy threshold was always set at 50 kev, and all energies above this level were counted unselectively by disabling the analyzer's upper discriminator. This is what is meant by the note on each scan: "Energies counted: 50 kev and over."

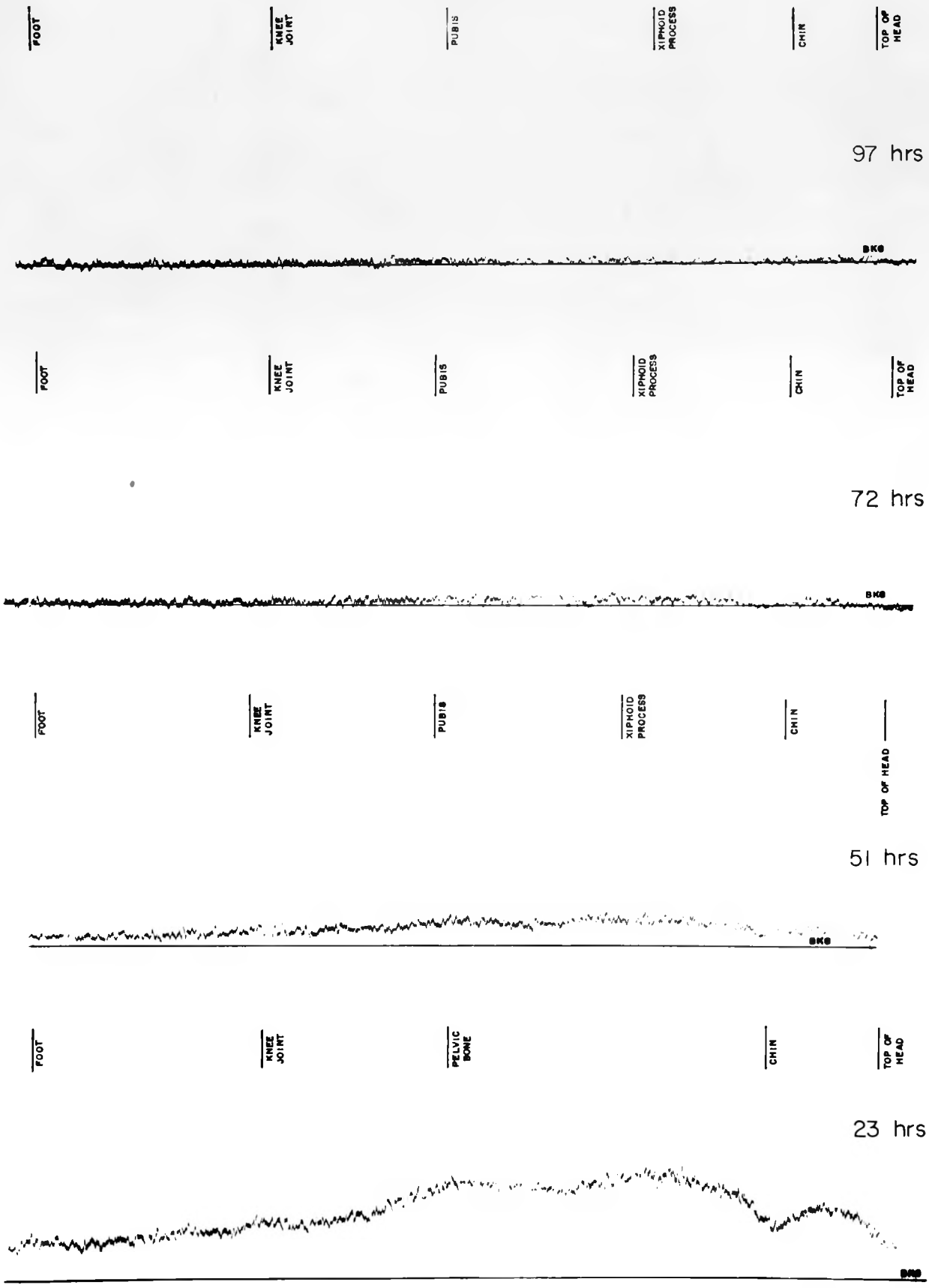
We may now pass on to a consideration of the actual scans. They have certain features in common. All have the same carriage and recorder speeds, so that none is more spread out than any other. All use the same one-inch collimator opening, the same 50-kev energy threshold, and, with a few exceptions, the same rate-meter sensitivities. The scans were run approximately every 24 hours for the first four days after the accident (June 16 at 2:00 P.M.); the elapsed times are shown, to the nearest hour, on the actual scans. Each patient's code letter and his estimated dose in rads are given at the bottom of the figure.

The scanner is provided with adjustable contacts at one side of the carriage, and these were used to correlate easily recognizable anatomical landmarks with the corresponding levels on the linear scans. We may assume that the designations "pelvic bone" and "pubis" refer to

the symphysis pubis. The other designations are less vague.

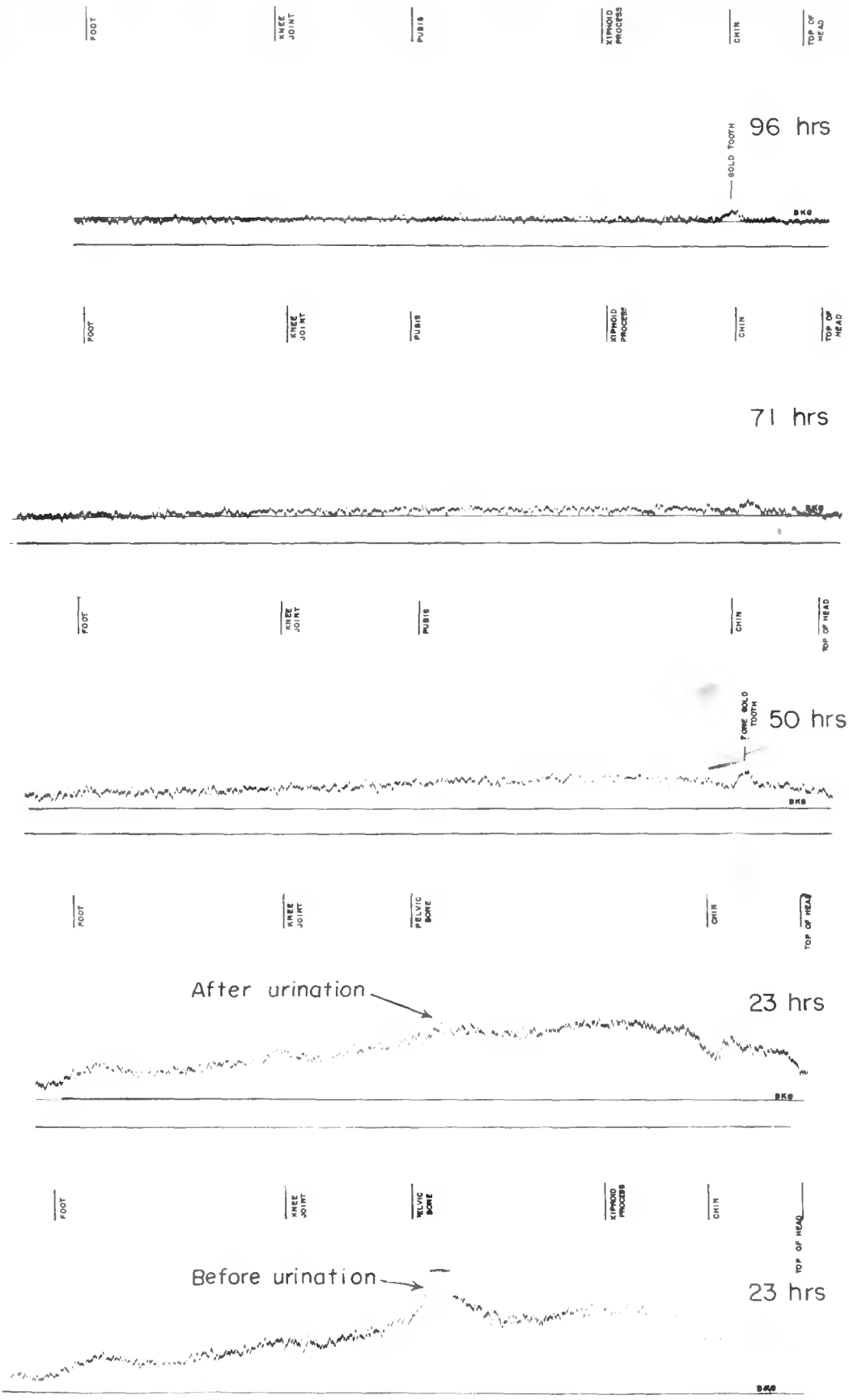
In some patients the bladder had not been properly emptied before the scan was started, and the "bladder hump" could be shown to disappear after urination (Patient B). In one patient (D) this did not happen, and investigation showed that the hump was due to a gold ring that he was wearing at the time of the accident, and was still wearing when the scan was made. The stable gold-197 had been activated by the neutrons to gold-198. Similarly, a gold dental inlay is responsible for the hump at the mouth level in Patient B; this hump is more persistent than the generalized activity, for the half life of gold-198 is 65 hours rather than 15. Patient D had a removable, gold-containing denture; when he took it out, the hump at the mouth level was much reduced. The spectrum of the "hot" denture was found to show the usual gold-198 photopeak at 412 kev.

Apart from these special features, the scans show generalized distribution of the activity throughout the body, the greatest count rates tending to be found at levels where the area of the transverse section is greatest. This is what one would expect on the basis of the sodium-24 hypothesis, for sodium is distributed generally throughout the extracellular fluids, with few local changes in concentration to upset the rule that the sodium content of a transverse section should be roughly proportional to the cross-sectional area. The reduction in activity shown in the successive scans is an index of the gradual disappearance of sodium-24 from the body, 1) through physical decay, and 2) through its renal excretion as it is "washed" out by stable, dietary sodium-23. As mentioned previously, the content of sodium-24 one day after the accident might be something like 10 microcuries, plus or minus a considerable margin for error.



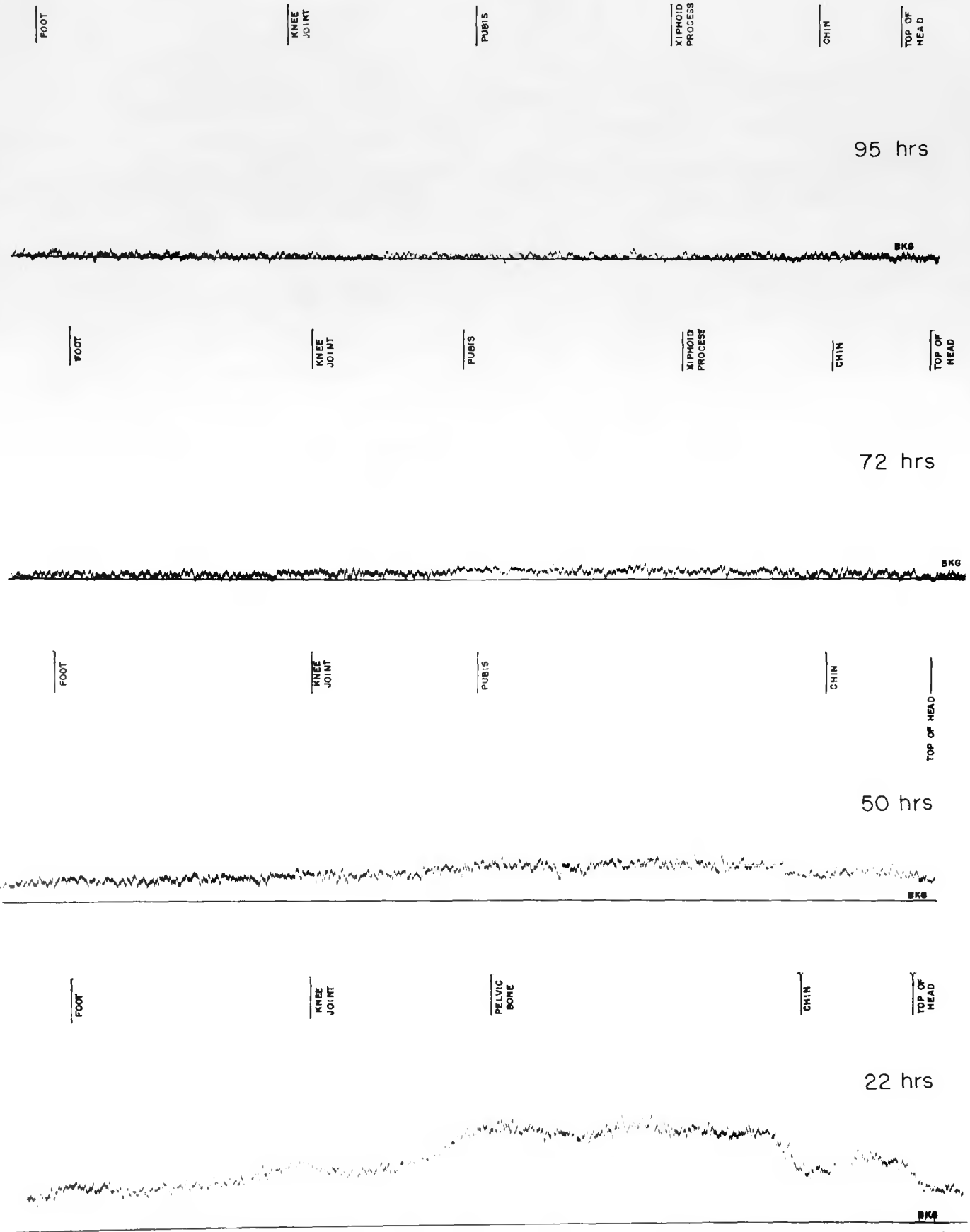
Energies counted: 50 kev and over

PATIENT A - 356 rads



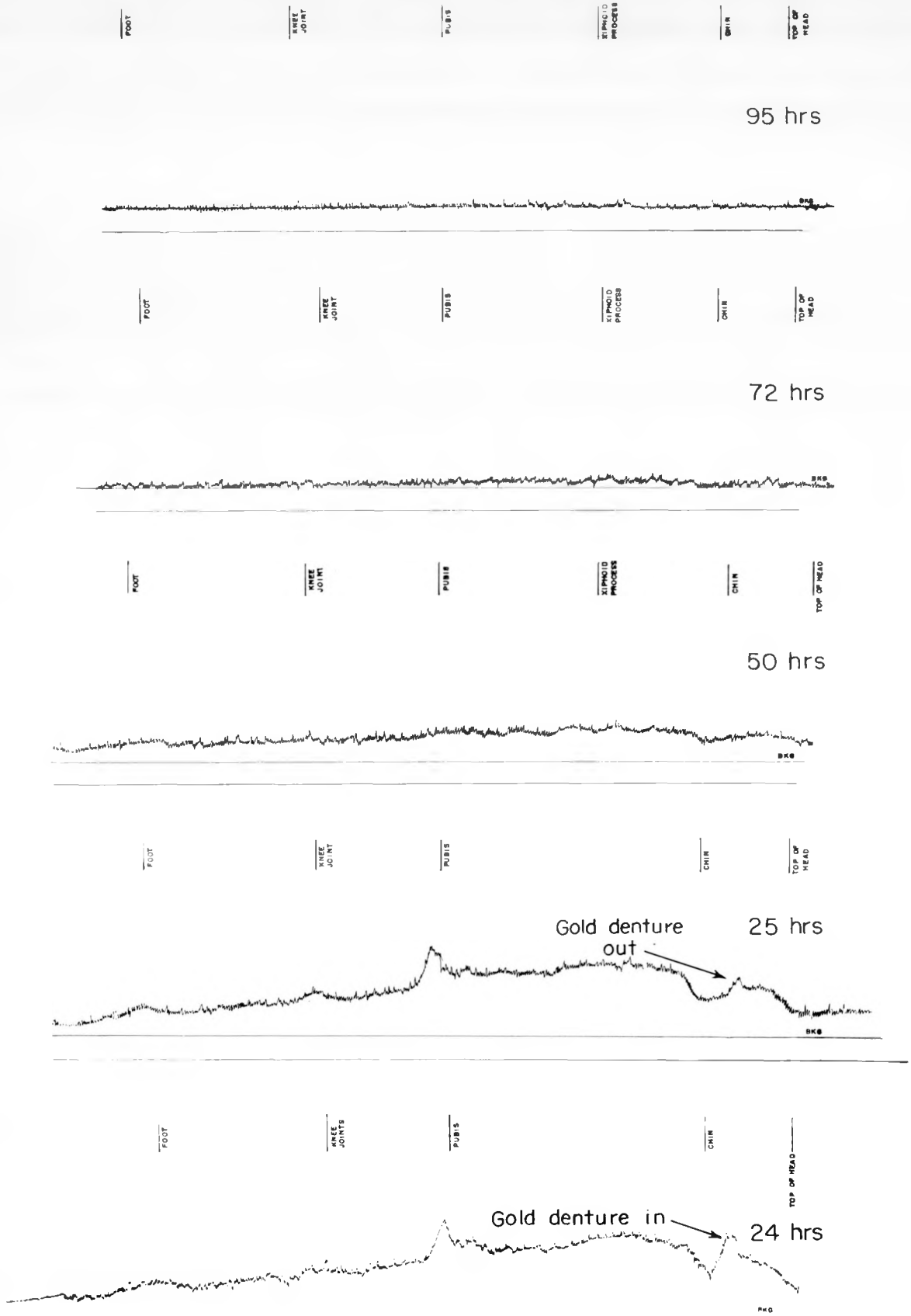
Energies counted: 50 kev and over

PATIENT B - 270 rads



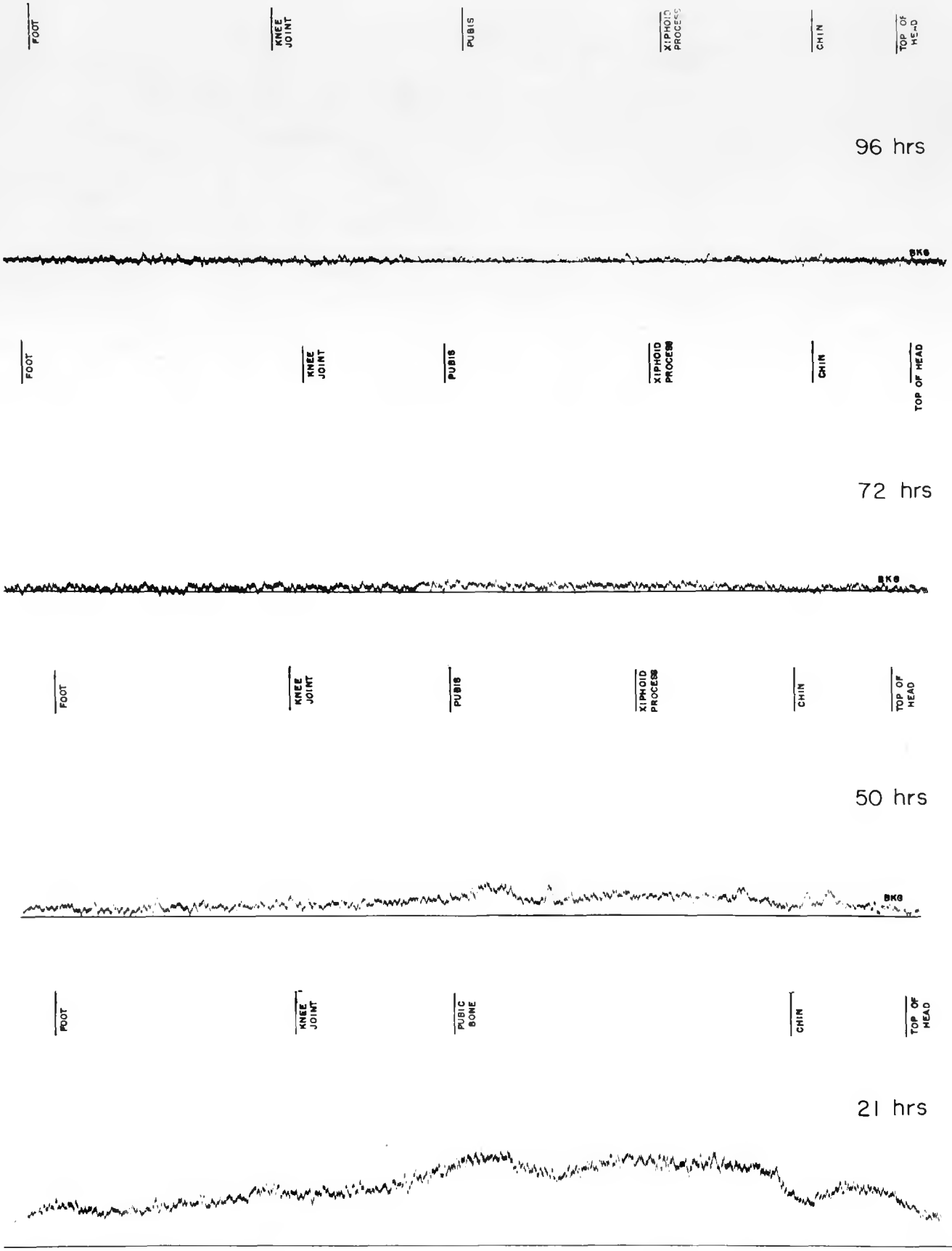
Energies counted: 50 kev and over

PATIENT C - 339 rads



Energies counted: 50 kev and over

PATIENT D - 327 rads



Energies counted: 50 kev and over

PATIENT E - 236 rads

RESPONSE OF THE BURRO EXPOSED TO AN EXPERIMENTAL NUCLEAR EXCURSION

U.S. Grant Kuhn, III
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During the years since 1877 (1) radiologists have attempted to quantitatively measure ionizing radiations. Various methods have included the use of the thermometer, ionization chamber, voltmeter, electroscope, various chemical systems, human skin, rabbit skin, the mouse, photographic emulsion, and most recently, the burro.

After the accidental human radiation exposure in Oak Ridge on June 16, 1958, a burro was exposed to a mock-up experiment in order to determine the neutron dose received by the affected persons. The conditions, design, and resultant calculated dose measurements are set forth in detail in a report by the Union Carbide Nuclear Company (2). The following is a comparison of the one experimental animal with the human cases and with results of previous animal experiments.

After base-line hematological examination, the subject animal (Jack No. 442) was placed in a wooden crate, hoisted into a position within six feet of the mock-up and exposed over a period of 42 minutes. He was observed to stand quietly throughout the procedure. The neutron dose received by the burro was determined from sodium activation in blood to be 48 rads, total-body. The gamma-neutron ratio of the mock-up assembly radiation was found to be 3.3/1; the neutron exposure plus gamma radiation therefore resulted in a total dose to the burro of approximately 206 rads.

The burro was returned to the holding pen and no behavioral change was noted before eight hours had elapsed. At that time the animal became anoretic and appeared restless and irritable. Three hours later it was necessary to anesthetize the animal in order that a whole-body

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counting procedure could be performed. On the following day the animal appeared somewhat subdued but resumed eating. During the ensuing three months there was no outward change indicative of illness or discomfort.

On the 15th day after exposure, epilation was noticeable on the side of the animal that had been nearest the mock-up. Within the next four days the loss of hair to the undercoat was complete (Fig. 1). The affected area was confined to the side, shoulder, and anterior surface of the rump. Within three months the affected area had shown normal regrowth.

The hematological response in the exposed burro was characterized by a nonspecific neutrophilic leukocytosis lasting throughout the 1st day. A decrease in absolute numbers of lymphocytes to less than 50 per cent of the preirradiation level was evident within one hour after exposure with lowest values at the end of a 24-hour period. After a transitory rise on the 11th day, the total leukocyte level continued to drop with the lowest observed value on the 30th day. Radiation leukopenia persisted through the observation period of 90 days. Serial changes in total leukocytes, segmented neutrophils and lymphocytes are shown in Fig. 2. The control values represent a four-month average of male burros.

Evidence of damage to the red cell system was presumed from the decrease in hematocrit and hemoglobin values in peripheral blood. Both reached lowest values on the 15th day postexposure. There followed a gradual increase to within normal limits by the 40th day postexposure. At 90 days there was again an indication of incomplete recovery (Fig. 3).

The platelet count of Jack 442 averaged 434,000 cells per cm during the 1st eight days postexposure. As shown in Fig. 3, the platelet count reached the lowest observed values on the 14th day (125,000 cells). The count remained depressed until the 75th day. At the end of the observation period the platelets remained below pre-exposure levels.

The response to ionizing radiation in the burro follows a rather definite clinical pattern, the severity of which is dependent upon dose and probably dose rate. It may also be affected by the type and quality of the radiation, but these we will think of in terms of modifying dose.

In nominal context with the last section of this report the following description of clinical response in the burro is included in order to broaden the bases for possible comparison between Jack No. 442 and the affected humans.

1. Lethality. The median lethal response of the burro has been determined for several isotopic sources to be from 532 to 784 r (3-5) and for a nuclear weapon (fission) to be 402 rep (6). There is some indication that the penetrability or linear energy transfer characteristics of the radiations influence the response. The neutron component

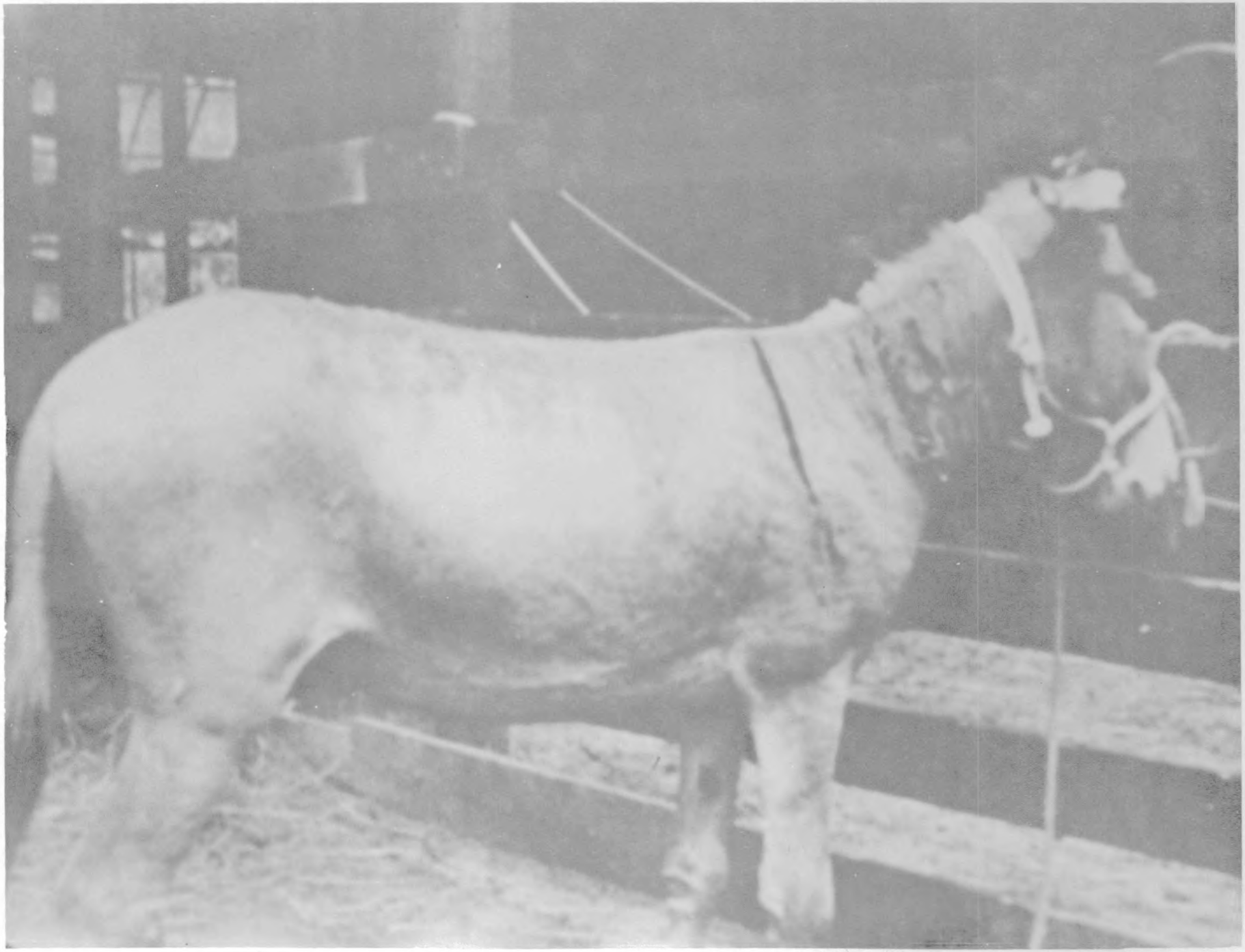

Figure 1. Epilation in Burro No. 442. Note well-defined area of shedding over rump, thigh, flank and side delimited anterior and posterior by vertical edges.

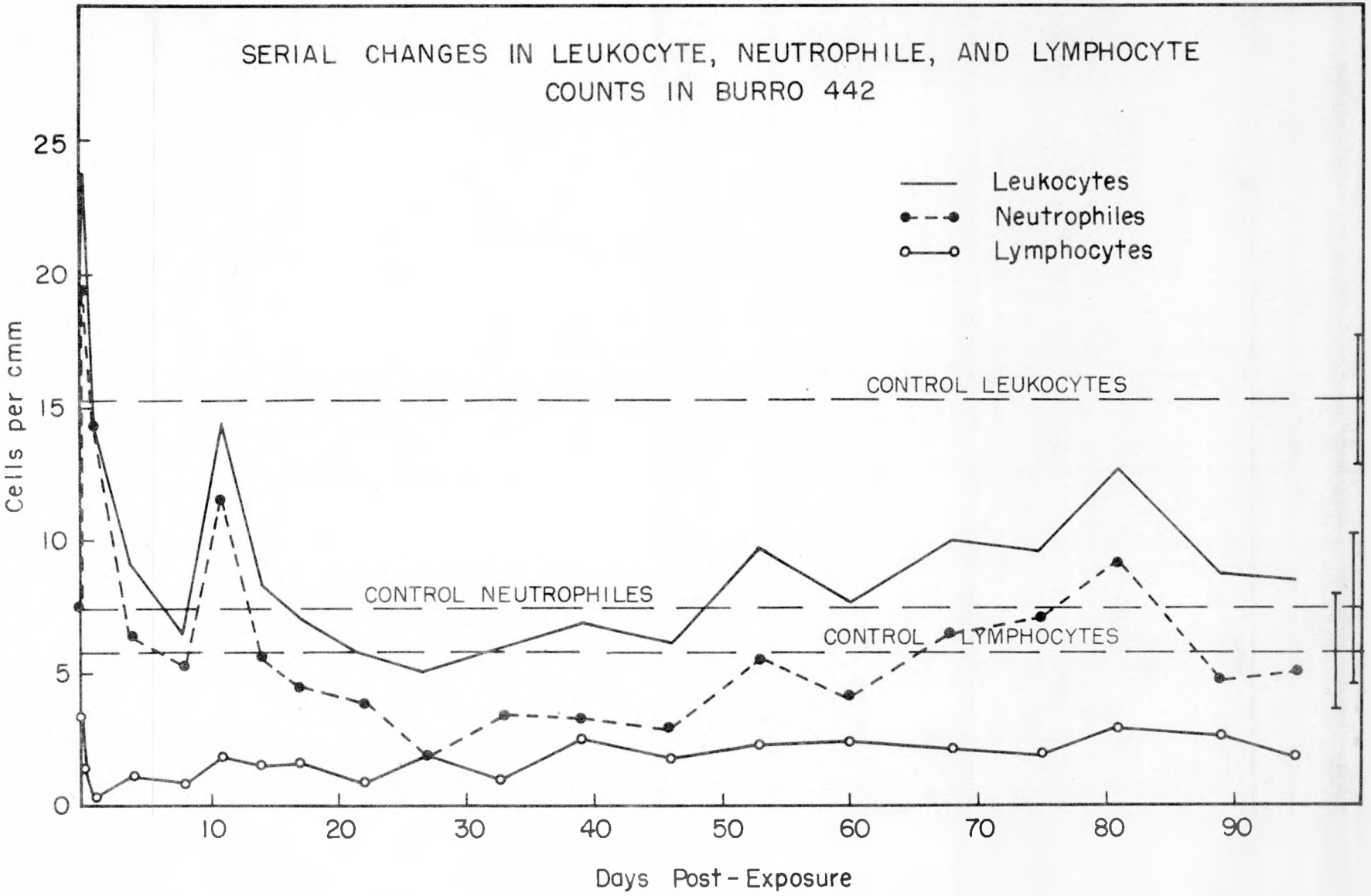
SERIAL CHANGES IN LEUKOCYTE, NEUTROPHILE, AND LYMPHOCYTE COUNTS IN BURRO 442
Leukocytes
Neutrophiles
Lymphocytes
CONTROL LEUKOCYTES
CONTROL NEUTROPHILES
CONTROL LYMPHOCYTES
Cells per cmm
0
5
10
15
20
25
10
20
30
40
50
60
70
80
90
Days Post-Exposure

Figure 2

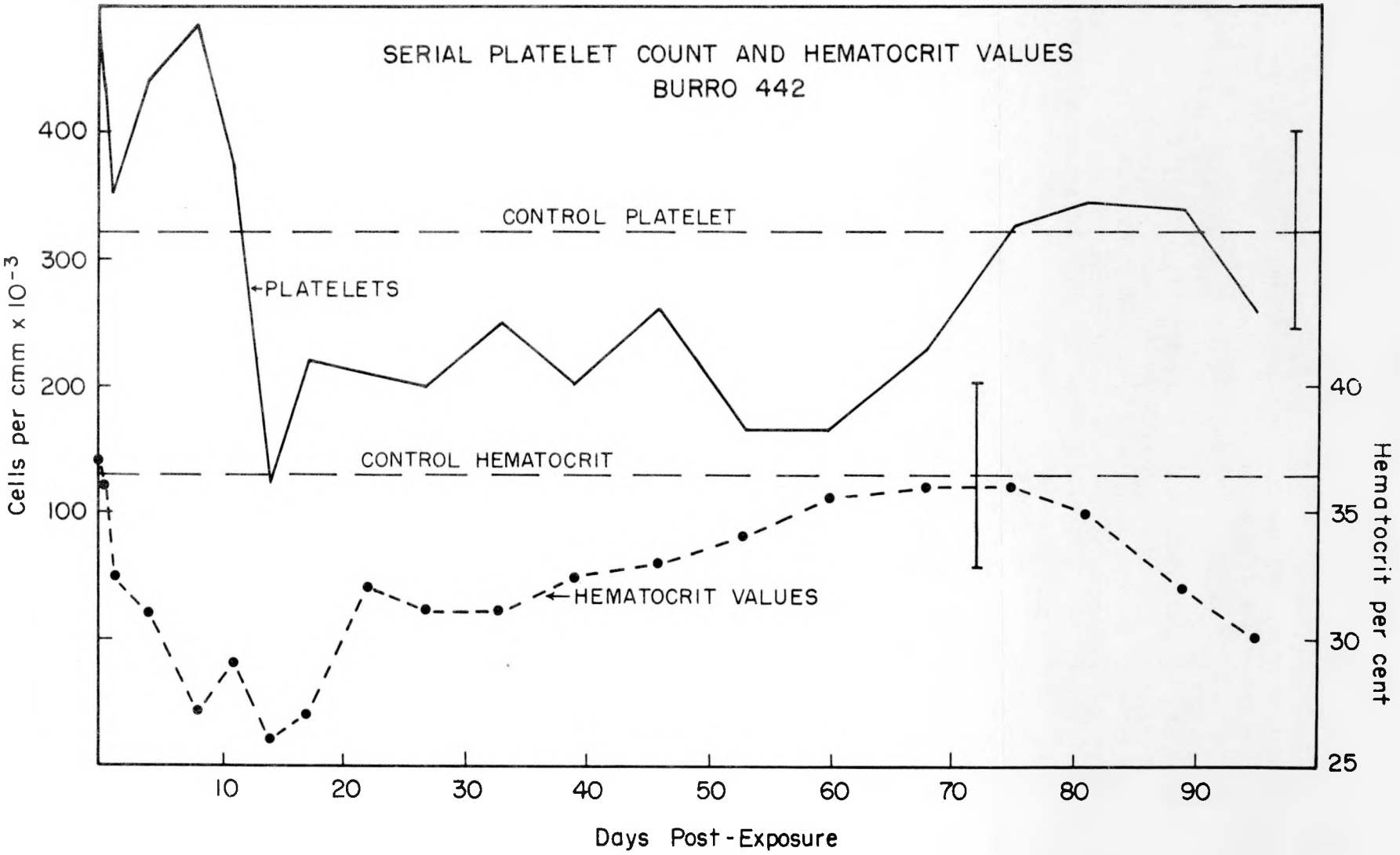
SERIAL PLATELET COUNT AND HEMATOCRIT VALUES
BURRO 442
CONTROL PLATELET
←PLATELETS
CONTROL HEMATOCRIT
←HEMATOCRIT VALUES
Cells per cmm x 10-3
Hematocrit per cent
Days Post-Exposure
400
300
200
100
40
35
30
25
10
20
30
40
50
60
70
80
90

Figure 3

of fission irradiation may have been more biologically effective than its counterpart gamma-ray emission.

Survival time of the burro after irradiation with midlethal-range exposures has been found to be variable and is possibly influenced by the rate of exposure. Irradiation with Zr-Nb^{95} and Ta^{182} at rates of 20 r/hr and 18 to 23 r/hr respectively have been followed by unimodal death patterns centering at 25 days postexposure. A bimodal death pattern with peaks at 3 and 26 days was observed after irradiation with Co^{60} at the rate of 50 r/hr. Similarly, a bimodal death pattern with peaks at 2 and 20 days followed the instantaneous exposure to mixed radiation from a nuclear detonation.

2. Subjective Behavioral Response. Except with very high exposure doses the irradiated animals show no immediate change but eat and act like normal animals. Often an early sign is lacrimation from one or both eyes. The first uniform change is depression with anorexia. Vomiting is rarely seen in equidae; however, during the initial depression drooling is seen. For a period of up to three days animals stand about with pendelous lips or make "mouthing" movements, ie., masticatory movements with smacking and licking of lips.

The period of depression may extend over several hours to several days. Usually a distinct irritability is manifested. Animals kick or bite at slight or no provocation during this time. Other signs of motor or sensory irritation, or both, may develop during the initial depression. After high exposure doses depression may proceed to convulsions and death within the first 24 hours. At midlethal levels of dose animals may exhibit other signs of nervous system involvement, such as hyperesthenia, muscle twitch, ataxia and orthochorea. Muscular weakness is a prominent sign following the period of depression-excitement.

The return of appetite is the first sign of subjective recovery and occurs within one to four days. An attitude of normalcy then prevails until the 8th or 9th day at which time diarrhea and anorexia are variously observed. During the following two to three weeks subjective recovery proceeds, dependent upon the degree of pathologic change present in the animal.

3. Hematological Change. During the first 48 hours after irradiation of the burro there may be a transitory neutrophilic leukocytosis; however, the initial hematological response is characterized by lymphopenia and eosinopenia followed to neutropenia and thrombocytopenia. Lymphocyte counts fall dramatically to lowest levels within 48 hours. Circulating neutrophils decrease less rapidly reaching minimum levels between the 3rd and 5th weeks. Platelets diminish after the 1st week and reach lowest levels between the 3rd and 5th weeks. Paralleling the platelet drop is a decrease in prothrombin utilization and clot retraction and a corresponding increase in whole-blood clotting time (7). Numerical recovery in circulating leukocytes and platelets is

protracted over the following two years.

Red cell decrease is maximum after 30 to 45 days in survivors of relatively high exposure doses and as early as 10 days after lower doses. Numerical recovery is usual by 10 to 15 weeks.

Certain physiological capabilities are clinically altered in relation to hematologic response. One of these is inflammatory reaction. Before the 8th day after irradiation, a reasonably normal inflammatory response to trauma is observed. Remarkable pus formation often follows infective processes. After the leukocytes have diminished to a level that will no longer support it, the inflammatory reaction is absent and even very septic wounds retain a fresh static appearance until death or until recovery again permits healing. At the time a clotting defect becomes manifest, prolonged bleeding occurs from the site of venipuncture, from old wounds, and even through intact skin. Purpura may appear spontaneously but is especially associated with the incidental trauma of handling. Ulcer formation in the digestive mucous membranes is frequently observed during and after the 3rd week. When present these ulcers are apparent in the mouth and anus; however, they may appear over the surface of the body, such as at the point of the hips, over the tuber coxae. At necropsy the earliest indication of ulcer formation is often in the caecum, near the ileocaecal valve or in the body of the organ in foci of parasite attachment. After hematologic recovery has been established, transitory increases in the leukocyte count will be noted in conjunction with incidental wound infection. Providing the animal body is successful in its defense, the leukocyte count returns to a level consistent with that existing before the rise.

4. Associated Causes of Death in Irradiated Burros. Animals that succumb within the early period (three days) following irradiation show no remarkable gross or microscopic change. In some animals abdominal laking of blood and lung edema are suggestive of a shock-like syndrome. Lymphocytic infiltration around small blood vessels in the brain invariably accompanies the encephalitis-like signs that appear before death.

Survivors of the 1st week may then die over the remainder of a 30-day period, showing evidence of the hemorrhagic phase of the irradiation syndrome. This may vary from well-defined purpura to massive visceral and muscular hemorrhage. Evidence of bacterial invasion is often demonstrated in animals that succumb during the hemorrhagic phase. Invariably there is no inflammatory reaction present even with severe infection.

After the period of the acute syndrome (30 to 40 days), deaths are associated with infective processes and blood dyscrasias. The latent effects observed in death two and one-half to seven years after irradiation have been primarily associated with aplasia.

5. Epilation. Epilation has not been seen in burros irradiated with pure gamma sources; however, exposure to the emissions of a fission-type nuclear detonation did cause epilation. Loss of hair was directly related to dose level and varied from almost complete denuding to marked shedding to the undercoat. In all animals the loss of hair was over a well-defined area including the back and one side. Epilation was observed at the lowest dose level, approximately 230 rads. The earliest appearance was on the 12th day with the bulk of cases observed during the 3rd week postirradiation. Regrowth of hair began after three months.

6. Temperature. No specific or constant changes in body temperature have been noted in burros after total-body irradiation with the exception of terminal fluctuation (8). The response to high dose-rate irradiation of the brain is characterized by increased (103 to 105°) temperatures throughout the first 15 hours.

These observations have been made on populations of experimental animals maintained in an unaltered environment that (as in Jack No. 442) received no supportive treatment nor augmentation of the normal dietary before or during the course of irradiation study.

There is presumptive evidence that the response of the burro to irradiation is similar in some respects to that of man (9). Indeed the primary objective of all foregoing irradiation studies with the burro is to obtain data useful in the extrapolation of effects to humans. As these comparative relationships become more clearly understood the present body of information on irradiation effects in burros and that occurring from the continuing studies of the species should become increasingly useful.

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STUDY OF THE PLASMA COAGULATION FACTORS IN VICTIMS OF THE Y-12 ACCIDENT AT OAK RIDGE

Jacques Gauthier, M.D., Robert Becker, B.S.
Herbert S. Sise, M.D. and John Bolger*

Hemorrhage has been an important and ominous sign in victims of extensive irradiation effects. Although its occurrence coincides with a period of intense thrombocytopenia, which alone could be the explanation of the bleeding, some evidence has been presented from time to time indicating that a circulating anticoagulant with heparin-like or antithromboplastic properties may contribute to the condition. Some controversy over the validity of the observations, however, indicated the need for further study using modern and reliable techniques.

The five subjects exposed to radiation in the Y-12 accident were studied on three occasions. The first study was 11 days after the accident. The second was the 29th day at the height of the period of thrombocytopenia. The only bleeding that had been observed was slight gum bleeding and petechiae in two, and gum bleeding alone in one other. The final study was on the 67th day when recovery had taken place. The following tests were done each time: Clotting time, prothrombin time (Quick), serum prothrombin, partial thromboplastin time (a test capable of detecting any of the known circulating anticoagulants as well as any deficiency of the plasma thromboplastic factors), thromboplastin generation test (platelet concentrations adjusted to a platelet count of approximately 300,000 in order to detect any qualitative abnormalities in the platelets), fibrinolysin (lytic effect of the euglobulin fraction on a standard preparation of human fibrinogen), and fibrinogen.

No abnormally low results were observed in any of the subjects at any of the studies with the one exception of a slightly abnormal thromboplastin generation (on one subject) which was believed to be due to

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difficulty in harvesting sufficient numbers of platelets during the period of thrombocytopenia. This defect was corrected by addition of normal platelets or the platelets from one of the other subjects. On the first study, however, fibrinogen levels were slightly higher than normal in all patients.

On both the first and second studies it was noted that the partial thromboplastin times of the subjects were very slightly shorter than those of the control subjects done at the same time. The partial thromboplastin times of the controls averaged 99 seconds and the subjects 83 seconds. This led to specific assay of the following plasma clotting factors: Prothrombin, proconvertin, Stuart factor, Ac-globulin, and antihemophilic globulin. This was done on the second and third studies. The observations were recorded in percentage of normal in reference to the normal control subjects of that day.

The results of these studies indicated somewhat elevated levels of Ac-globulin in four of five patients and distinctly high levels of antihemophilic globulin in all patients at the time of the second study, which was at the peak of the thrombocytopenia. At the third study, during the period where bone marrow recovery had taken place, the values had returned to normal levels. In one instance (Patient E) the AHG level dropped to slightly below the normal range of 60 to 100 per cent. It is doubtful that any significance can be placed on this isolated finding. A summary of the results is shown in Table 1.

It seemed obvious to suspect a relationship between low platelets and supernormal values of AHG and Ac-globulin. Consequently, the studies were repeated on other patients with low platelet counts. Seven cases of either idiopathic or secondary thrombocytopenia were studied. The results are shown in Table 2. Here the Ac-globulin was found to be elevated in only two cases and normal in the rest. The AHG level, however, was increased in all but one and was over 300 per cent in three patients.

The explanation of the supernormal values in the Y-12 victims would therefore seem to be related to the low level of platelets rather than due to any direct effects of irradiation. One obviously possible mechanism would be that the well-known adsorptive capacity of the platelets for these two factors was responsible. If a given amount of the total circulating Ac-globulin and AHG are adsorbed on platelets, then when normal blood is centrifuged to harvest the plasma, a portion will be sedimented with the platelets. If there are deficient platelets in the blood, however, there will be less of the factors adsorbed and sedimented and more will remain in the supernatant plasma. This hypothesis was tested by mixing platelet-rich hemophilic plasma, which conceivably would have platelets that would not be saturated with AHG, with normal platelet-free plasma. After various periods of incubation this mixture was spun down and the remaining AHG concentration of the supernatant was tested. As a control, platelet-poor hemophilic plasma was

similarly added to normal plasma. It could not be shown that AHG was adsorbed on the platelets in this manner.

Another possible but less attractive hypothesis is that when the platelet level is low there is less intravascular "clotting" and consequently the turnover rate of clotting factors is slow, allowing an accumulation in the plasma. This seems unlikely, since no supernormal values for any of the other clotting factors could be demonstrated.

In summary, investigations of the clotting mechanism in these irradiated subjects showed no defects or circulating anticoagulants. No fibrinolysis was apparent. On the contrary, the surprising finding of supernormal levels of Ac-globulin and AHG were noted in the period where the thrombocytopenia was at its peak. Slightly elevated fibrinogen levels were observed in the acute phase (11 days). It was concluded that the supernormal values were secondary to the thrombocytopenia and not due directly to the effects of the irradiation.

Table 1

	Ac-Globulin (% of normal)			AHG (% of normal)			Fbg (mg/100 ml plasma)			Platelets/mm^3 Average values for the 5 patients		
	6-27-58	7-15-58	9-22-58	6-27-58	7-15-28	9-22-58	6-27-58	7-15-58	9-22-58	6-27-58	7-15-58	9-22-58
Patient (C)	-	168	132	-	276	124	500	417	316			
Patient (D)	-	148	104	-	220	146	538	353	228			
Patient (E)	-	168	136	-	248	52	610	232	285	190,000	30,000	235,000
Patient (B)	-	124	112	-	220	106	538	480	518			
Patient (A)	-	168	128	-	234	88	558	465	317			
Normal	-	108	108	-	100	102	441	312	302			

Table 2

Ac-Globulin, AHG, and Fibrinogen Levels in Patients with Idiopathic and Secondary Thrombocytopenic Purpura

Patients	Platelets/mm^3	AHG % of normal	Ac-Globulin % of normal	Fbg mg/100 cc plasma
1.	15,000	> 400%	172%	245
2.	21,000	> 400%	81%	382
3.	35,000	200%	80%	176
4.	22,000 14,000 39,000 50,000	150%	150%	394
5.	51,000	100%	124%	240
6.	9,000	150%	100%	346
7.	25,000	314%	108%	600

PERSONNEL RADIATION MONITORING FROM A CRITICALITY ACCIDENT

H. F. Henry*

Introduction

A criticality accident imposes special conditions upon the methods used to determine the resultant radiation exposures of nearby personnel. These involve basically the necessity for prompt identification of those few who have been rather seriously exposed in order that they can quickly be given the necessary medical attention, it being very desirable that exposures greater than 100 rads be identified accurately, probably to within 100 rads, especially in the exposure range of 400 to 500 rads.[1] Concurrently, a determination must be made that other personnel, who will comprise the vast bulk of employees at an industrial establishment, have definitely received either no exposures or sufficiently low ones that they require no special consideration other than that given for routine on-the-job radiation exposures. Although probably not of equal urgency, administrative decisions concerning the facilities involved and an evaluation of control actions available will also profit by this prompt exposure determination.

In general, an accurate determination of radiation doses requires information concerning exposures due to fast neutrons, slow neutrons, and gamma radiation. This may, of course, involve direct measurement of only one of these items, and determination of the others therefrom by use of additional data determined previously, at the time of, or following, the incident. Thus, it is the purpose of this brief report to suggest a comparatively simple personnel monitoring system, which appears to be capable of providing as complete and accurate information as will probably be possible for any external monitoring system. The brief discussion also includes comments concerning the problems involved

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* Safety, Fire, and Radiation Control Department, Union Carbide Nuclear Company, Division of Union Carbide Corporation, Oak Ridge Gaseous Diffusion Plant, Oak Ridge, Tennessee.

1 Brucer, Marshall, An Interim Report of the June 16, 1958, Y-12 Accident, 8/8/58, mimeographed.

in monitoring units or systems, which have been used or suggested.

Discussion of Monitoring Requirements

Current Devices

Methods. The direct monitoring of the gamma or neutron radiation, or both, from an accidental radiation burst appears to be the most feasible method for exposure evaluation. Hence, devices that can be activated by these radiations are normally considered practicable for this monitoring. In addition, administrative conveniences concerned primarily with employee acceptance and willing use have generally dictated that any external monitor be small and light, thus confining its use to a single position on the person's body as in routine film meter monitoring.

Neutron Activated Foils. Of the various possibilities, the only current device specifically designated as a monitor for a possible criticality accident is the indium foil that has been used in the security badges at the Oak Ridge Gaseous Diffusion Plant (ORGDP) since 1950,[2] at Y-12 since 1954,[3] and at the Paducah and Portsmouth Gaseous Diffusion Plants since startup; at the time of the Y-12 incident,[4] this device completely and effectively fulfilled its basic specified function of promptly identifying those personnel who had received significant radiation exposures, and, with proper calibration based on the most recent information, gave dose evaluations within the general range of those determined by other methods. The wide variations in actual estimated doses and even rank order of injury as determined by various methods, compared to clinical findings, are indicated in Tables 1 and 2. It may be noted that in comparison with other results obtained, the indium foil values were well within the possible deviations originally recognized as being inherent in this monitoring method.

In addition to indium foils, the use of other neutron-activated materials, such as tantalum, sulfur, or gold, have been suggested for

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2 See letter from H. F. Henry to A. P. Dunlap, Proposal for Monitoring of Personnel in the Event of a Radiation Accident, dated 5/26/49, and K-25 Plant Quarterly Report for Fourth Fiscal Quarter, April 1 - June 30, 1950, Part E 8/15/50 (K-636). Technical details are given in two reports: Rohr, R. C., and Henry, H. F., The Energy Spectrum of the Leakage Neutrons from a Homogeneous Reactor, 7/5/51 (K-736). Bailey, J. C., Henry, H. F., Rohr, R. C., Calibration of Indium Foils for Personnel Monitoring, 6/1/53 (K-999).

3 Wachter, J. W., and Emerson, L. C., Neutron Dose Calibration of Indium Personnel Dosimeters for Prompt-Critical Metal Bursts, 3/1/56 (Y-1092).

4 Patton, F. S., et al., Accidental Radiation Excursion at the Y-12 Plant, June 16, 1958, 8/4/58 (Y-1234).

similar monitoring; in fact, at the time the indium was selected, silver and manganese were also tested.[2]

Body Fluid Analysis. Evaluation of the neutron activation of the sodium in the body of an exposed person has formed the basis for monitoring methods based upon direct radiochemical analysis of blood, urine, or the use of a "whole-body counter."

All the methods noted were used in the Y-12 incident, the evaluation of the blood sodium, properly calibrated, being reported as probably giving the best value for the actual exposures of the personnel involved. Table 2 summarizes the exposures reported for the various methods.

Other Methods. In addition to monitoring by means of neutron-activated materials, exposures should also be determinable from gamma activation of film meters or other gamma-sensitive materials, colorimetric methods being also specifically suggested. There are, of course, various methods of calculating exposures as based upon information concerning the reacting system, distance of the employee from the source of radiation and other variables.

Problems in Dose Evaluation

Basic Problem. The basic problem in determining radiation exposures by any device or method is the fact that the radiation dose measurement recorded thereby may not correctly reflect the actual radiation dose incident upon the person exposed; it may be noted that radiation effects are normally expressed in terms of this incident dose. In addition, the immediate environment of the person exposed, the position of his monitor, or his body itself, may so alter the radiation affecting the indicator that its response may not correctly reflect the incident radiation by factors of two or three at least. In ordinary routine monitoring, these unevaluated variables are, in general, "averaged" out by the person's actions in the radiation field itself and the fact that most routine week-long exposures are the sum of many smaller exposures received randomly during the monitoring period. In addition, the permissible dose limits themselves are probably sufficiently low and the safety factors used in determining them sufficiently conservative that no injury or other damage might be anticipated by control based on the measured doses, even in the absence of this "averaging." However, it is apparent that an evaluation of these factors, or their elimination, could obviously be extremely important where single high exposures dangerous to life itself are concerned. Some of these factors are briefly described. It will be noted that, in general, all of them basically involve the energy response of the monitor or the position of the person involved.

Attenuation. A major consideration in dose evaluation is the fact that the attenuation of radiation in passing through a human body can result in indicated exposures varying by factors of 2 to 13 for indium foil neutron detectors[5] or 2 to 10 for gamma film meter detectors,[6] depending on whether the person concerned is facing the reaction or has his back thereto. Similarly, scattering of radiation from adjacent walls, items of equipment, etc., can affect the monitor reading by factors up to four for neutrons[7] or small percentage factors for gammas,[6] when the same monitoring methods are used.

"Moderation." Most neutron-activated materials are much more sensitive to low-energy neutrons (including thermal) than to fast ones, and the response of most film meters to gamma radiation depends upon the gamma energies although reasonably effective compensation for these differences is usually possible. Thus, any exposure wherein the energy spectrum of the incident radiation is different from that striking the monitor will result in an indicated exposure different from that actually received. This is a particular problem with neutron detectors, since many substances including the person's body itself, contain significant amounts of hydrogen and thus have the property of moderating, or slowing down, fast neutrons; thus, it is practically impossible for the neutron spectrum incident on a human body to be correctly reflected by any device he may wear. For example, indium foil monitors placed upon a human body will have readings up to a factor of at least seven different from a similar foil exposed in air; this has been noted for reacting systems involving both metals and solutions.[7] Energy spectrum changes are also possible as a result of scattering from adjacent items of equipment, etc., although in this case, of course, the scattered radiation is actually also incident upon the person involved. It may be noted that there are apparently few data available for evaluating similar possible gamma-energy spectrum changes.

Special Factors in Body Fluid Checks. Although direct analysis of body fluids or the use of body counters, if well calibrated, should reduce the effect of some of the factors of concern for external monitors as noted above, these factors probably cannot be eliminated completely, and these methods themselves can introduce additional problems which are primarily involved in the variabilities of human, and other biological, systems. For example, as indicated previously, the thickness of a person's body can be a factor. In addition, for many of the blood constituents, "normal" conditions can frequently involve variation ranges of 30 per cent to 100 per cent, although a similar variability should not be anticipated for blood sodium. However, it does appear that careful and accurate calibration should permit this

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5 Conclusion drawn from data in Appendix II of Y-1092. (Ref. 3) Similar experimental data are given in Table 1 of K-736. (Ref. 2)
6 Unpublished experimental work at the ORGDP.
7 Conclusion drawn from data in Appendix II of Y-1092. (Ref. 3)

method to eliminate more of the uncertainties than any of the others proposed. With respect to the "whole-body counter," it does not appear that this method can be as accurate as the body fluid analysis method and may very well be no more accurate than the various external monitoring systems.

It should be emphasized that many of the previous comments are based upon the very limited data available, some still unpublished. However, it does indicate that there are serious problems in developing a simple monitoring device or system for use under the conditions involved in a critical reaction. It may be noted that no attention has been given to the different time factors involved in making determinations by the various methods. These are, or may be, themselves significant considerations where large numbers of persons are involved. This is probably particularly true for the "whole-body counter" method.

Proposed Monitoring System

General. The attached diagram (Fig. 1) indicates a proposed monitoring system. Briefly, it consists of a comparatively simple personnel monitoring device worn by an employee, coupled with an area-type monitor incorporating an accurate neutron-gamma spectrum analyzer and dose detector accompanied by a calibrator for the employees personnel monitor. It may be noted that various types of area monitors have been used or proposed for diverse purposes and various personnel monitoring devices have been widely used. It is proposed that the area-type monitors be placed at arbitrary points throughout the area of concern, say on 100-feet centers, and that all employees and visitors be required to wear or carry the personnel monitor at all times.

Function of Area Monitor. This unit will be designed to provide accurate information concerning the neutron and gamma doses received at the point of installation. In practice, the neutron detecting unit of the neutron-gamma area monitor will probably be composed of metal foils and shields so selected as to provide information both of the neutron-energy spectrum and the actual neutron dose at the point of installation. Several different types of energy-discriminating devices have been reported in the literature.[8] The gamma detecting unit will probably

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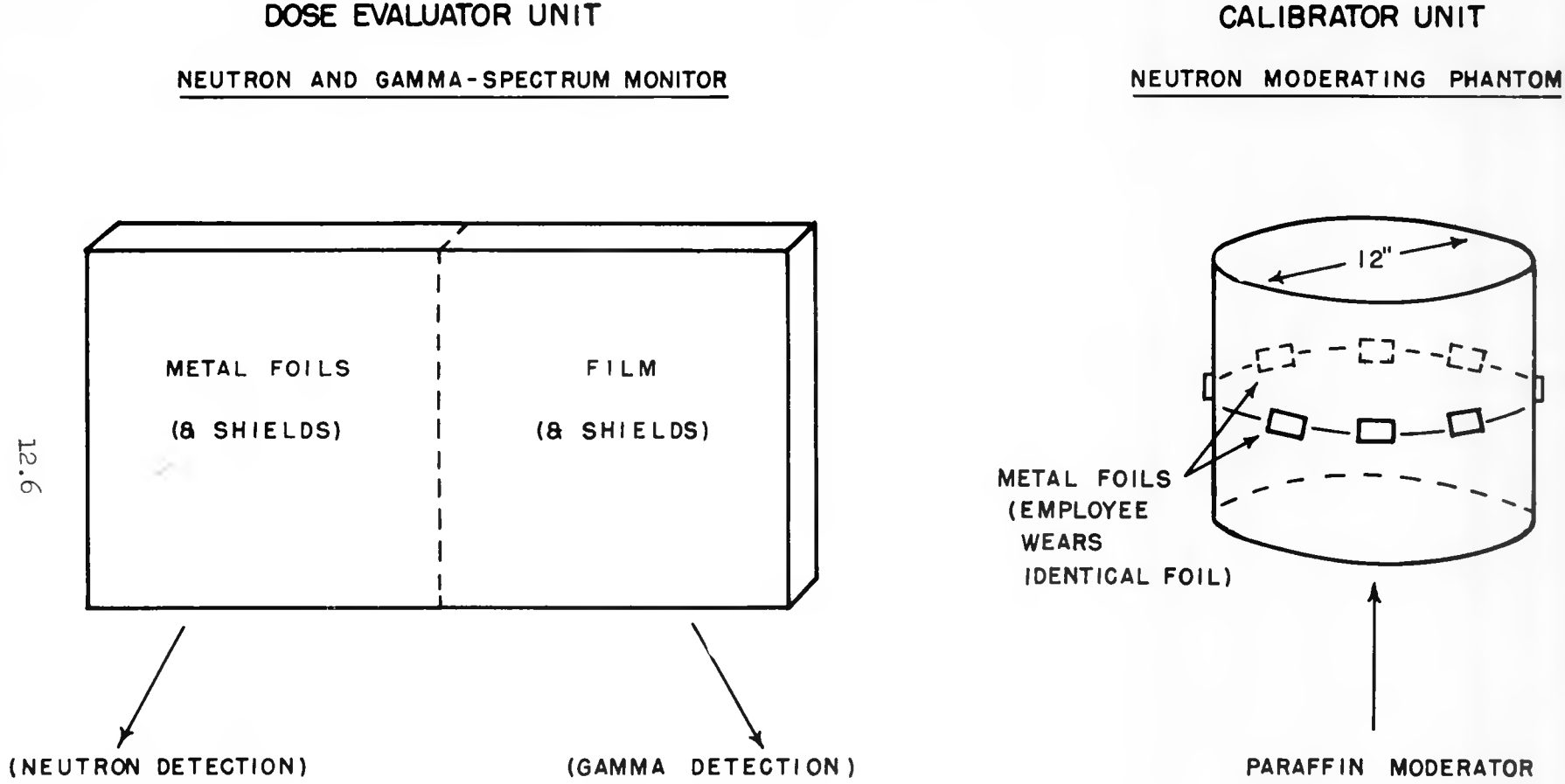
8 See, for example,
Fitzgerald, J. J., and Detwiler, C. G., Resonance-Threshold Foil Neutron Personnel Dosimeter, 6/8/56 (KAPL-1516).
Hurst, G. S., et al., Techniques of Measuring Neutron Spectra with Threshold Detectors - Tissue Dose Determination, The Review of Scientific Instruments, Vol. 27, No. 3 (March 1956), pp. 153-156.
Sayeg, J. A., and Harris, P. S., Experimental Determination of Fast- and Thermal-Neutron Tissue Dose, January 1958 (LA-2174).
Trice, J. B., Measuring Reactor Spectra with Thresholds and Resonances, Nucleonics, Vol. 16, No. 7 (July 1958).



12.6

FIGURE I. AREA-TYPE NEUTRON AND GAMMA-DOSE EVALUATOR

involve a film meter with appropriate shields to identify the gamma spectrum and the actual gamma dose. This entire dose detector also may, or may not, include the personnel monitoring device worn by the employee.

Function of Calibrator Unit. The calibrator section of the area monitor will consist of units of the personnel monitoring device placed around an appropriate body "phantom"; this may be a one-foot diameter cylinder of paraffin, which has possibly been modified to incorporate materials making it chemically similar to a human body. The purpose of this unit would be the translation of actual dose, as determined by the neutron-gamma area monitor, into terms of the reading of the personnel unit worn by the employee. In itself, it might also serve as a reasonably accurate dose indicator[3] at its point of installation.

Function of Personnel Monitor. The personnel monitor worn by the employee should have a basic purpose of providing a very rapid means for separating those who may have received serious exposures from those with slight, or no, exposure, and should also give as accurate information as feasible concerning the actual exposure of the employee. If possible, it should also meet such administrative criteria as simplicity, ease of use, and be of such acceptability that all employees will normally wear or carry it. The indium foil currently used in the security badges of various installations meets these general criteria as well as any other and is probably entirely adequate for this use, although, of course, better materials may be available, and this should be thoroughly investigated.

Use of System. In using this system, the employee's monitor would be read as soon after the accident as possible to provide a means for determining those employees who were seriously exposed; simultaneously, several of the neutron-gamma area monitors would be taken from locations as close to the reaction and the employee's position as feasible. From the accurate dose information obtained from the neutron-gamma area monitors, calibration curves relating these doses to the activation of the calibrator units may be determined. In turn, the readings on the employee's monitor would be used with these calibration curves to determine his exposure range. Although this range can easily involve differences of the order of a factor of three or four, reasonably accurate information concerning the employee's actions at the time of and after the incident, as well as the course of the reaction, may permit considerable narrowing of this range of uncertainty.

It may also be noted that the neutron-gamma detecting area monitors could also be used to provide an indication of the dose-field in which the employee was and this could serve as a reasonable check upon the dose which he actually received.

General Aspects of Monitoring Systems. Although it is possible to provide a personnel monitor that would comprise a comparatively complicated system of neutron and gamma detectors, complete with energy

analyzers, its value appears somewhat questionable, especially if its use would complicate or slow down the actual dose determination or reduce the acceptability of the personnel monitor to plant personnel. It does not appear that any personnel neutron monitor of this type would overcome the basic difficulties produced by the shielding and moderation effects of the wearer's body much better than the simple monitoring device currently available. Similarly, any film meter use would be subject to the corresponding difficulties as noted above. In addition, the use of a combined neutron-gamma monitor in the personnel unit does not appear to provide a significant improvement over either type alone. The principal advantage of such a unit over either singly would be the accurate determination of the neutron-gamma dose ratio, and this information should be most accurately and readily available from the area monitors themselves; this would also obviate the inaccuracies in this ratio produced by the differing effects of the wearer's body upon these respective radiations as noted previously. Although neutron emission occurs only during the actual reaction, gamma emission occurs both during the reaction and afterwards with the result that the neutron-gamma exposure ratio will be somewhat different if the exposures occur only during the reaction or if they also occur partially during a subsequent period. However, as indicated in Y-1234, the immediate gamma-neutron dose value for the system concerned was about 2.8 whereas it was about 3.3 when the subsequent gamma exposure was included. Thus, it does not appear that exposure uncertainties due to this difference would be significant in comparison to others as previously described.

It should be particularly noted that the variabilities involving an employee are such that any external monitoring device or system can, at best, give only reasonably accurate indications of the exposure of the person, and the most accurate information should be available from analyses of his body fluids. Thus, the greatest usefulness for any external monitoring device should occur in the period before the availability of more accurate information.

Available Calibration Information.

With respect to the preceding comments concerning the validity of the various monitoring systems, it should be emphasized that, of the systems available, it appears that only the indium foil has been sufficiently well calibrated that its limitations and limits of error have been recognized, and these were discussed in the original technical reports.[2,3] Thus, the previous comments concerning the relative effectiveness of monitoring methods are based largely upon rather qualitative analyses of what should be the case, and further careful study may indicate differences in the dose-determination accuracies possible with the various ones.

Regardless of the materials or methods chosen for a monitoring system of this type or any type, thorough and complete calibration is imperative.

Conclusions

1. Based upon available information, no single, simple monitoring device or method can or will provide sufficiently accurate information (concerning a person's actual exposure at the time of a criticality incident) of significant value to the medical treatment of the highly exposed person. However, the indium foil (currently used in security badges) is adequate for the very important rapid separation of seriously exposed persons from those relatively slightly exposed persons in even a large plant population.

2. Published basic data of value in relating the results of monitoring devices or methods to actual exposures are lacking to the extent that no device or system now in use or proposed can be said to be accurately calibrated for the conditions of an accident, although the limitations of the indium foil method have been recognized and reported.

3. From a qualitative review of the over-all problem, it appears that analyses of body fluids should provide the most accurate information concerning an actual exposure, and an external monitoring system should be of greatest effectiveness before this information becomes available.

4. It seems that the monitoring method proposed, which involves use of a simple metal foil-type personnel monitor along with area monitoring units, not only will provide as accurate information as is possible from an external monitoring system but also will be readily acceptable to personnel.

5. The method proposed, as with all monitoring methods available or proposed, will require extensive evaluation, testing, and calibration for effective use.

Table 1

Rank Order of Dose Estimates

Name	Clinical Estimates				Body Fluid Analysis			Other Methods			Calculations	
	Over-all			Hematology	Blood	Urine		Indium Foil	Total Body Counter		Charpie	Morgan
	5th Week	3rd Week	1st Week	1st Week		(Sodium)	(-)		(Preliminary)	(Final)		
A	1	1	1	1	1	1	2	3	2	1	1	1
C	2	3	5	4	2	3	4½	2	1	2	3	4
E	3	2	2	2	5	5	1	1	3	4	5	5
B	4	4	3	3	4	2	3	5	5	5	4	2
D	5	5	4	5	3	4	4½	4	4	3	2	3

Note: All figures are taken from Y-1234, "Accidental Radiation Excursion at the Y-12 Plant, June 16, 1958", (Final Report) 8/4/58; Y-1199, "Accidental Radiation Excursion at the Y-12 Plant, June 16, 1958", (Preliminary Report), 6/25/58; or "An Interim Report of the June 16, 1958, Y-12 Accident" by Marshall Brucer, M.D., 8/8/58.

Table 2

Dose Estimates (Total Rads)

Name	Body-Fluid Analysis			Indium Foil	Whole-Body Counter	Calculations	
	Blood		Urine				
	"Burro"	Calc.	(Sodium)			Charpie	Morgan
A	365	274	270	182	528	276	1330
C	338	258	233	190	505	230	175
E	236	175	165	213	391	163	110
B	270	201	241	118	296	188	228
D	327	243	228	152	407	239	201

Note 1: The results of calculations by Charpie and the urine analyses are taken from "An Interim Report of the June 16, 1958, Y-12 Accident" by Marshall Brucer, M.D., dated 8/8/58. All other dose values are obtained from data in Y-1234, "Accidental Radiation Excursion at the Y-12 Plant, June 16, 1958", (Final Report), 8/4/58.

Note 2: With the exception of the results of calculations by Charpie, which are listed as reported, all values are taken from the reported neutron dose only and the consideration that the gamma/neutron dose ratio is a constant of 2.8. Thus, the Total Dose = Neutron Dose + 2.8 Neutron Dose. The figures thus differ from those given in the reports. No attempt to use an RBE $\neq 1$ was made.

THE ACUTE RADIATION SYNDROME

Marshall Brucer, M.D.

Introductory Explanation of Method of Presentation. Fortunately, or unfortunately, depending upon your position in regard to a radiation accident, the medical profession does not have sufficient evidence to outline a detailed description of the acute radiation syndrome in man. This is fortunate in that there has been such a great emphasis on radiation safety that the medical profession has seen far fewer accidental exposures than should ordinarily be expected in an atomic energy program of the magnitude of that in the United States. It is unfortunate in that when an accident does occur the physician who has the responsibility for the patient is going to have to proceed on the basis of guesses. Some of these are well-educated guesses because there has been a significant amount of animal work on a related problem - that of the radiation effects of military weapons. Some of these guesses, however, are not even well-educated because the experimental work differs in so many respects from that in man.

Physicians are used to dealing with the application of new drugs. In a sense these are poisons in the same way that radiation is a poison. Usually, however, new pharmaceutical agents are reasonably well known before they are applied to the human. In total-body irradiation the situation is not so well known. There is a delay in the action of any drug; however, in radiation this delay is exaggerated. The dose of pharmaceutical agents is controlled. In radiation accidents we are talking about an uncontrolled dosimetry ranging from very small to very large doses.

Therefore in the presentation of the effects of radiation, the dose-time relationships become of exceedingly great importance. It is impossible to talk about radiation effects without talking about the effect in a dose-time matrix. All the effects described here are described in terms of a three-dimensional dose-time-effect matrix. This kind of presentation has necessitated the preparation of three-dimensional charts.

The charts are made in the following way (see illustration): Using as an example the total white blood cell counts following an

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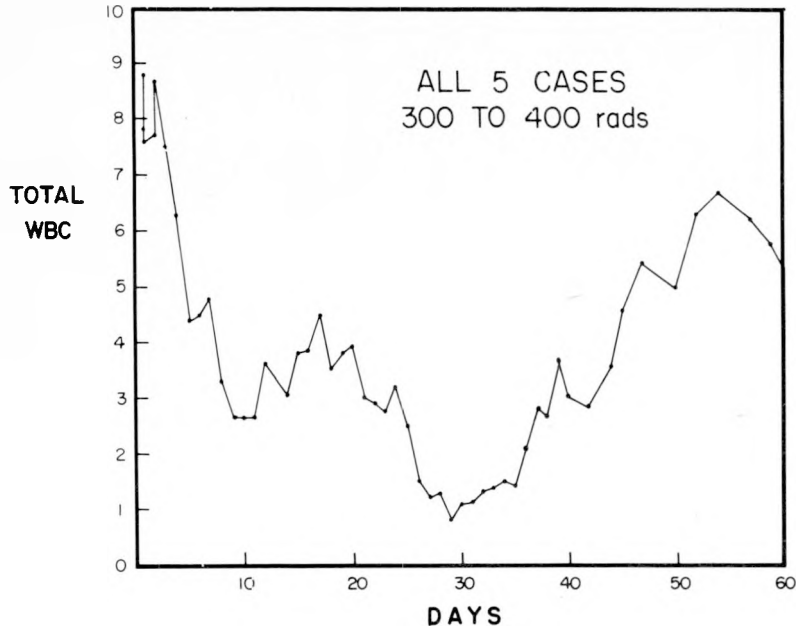

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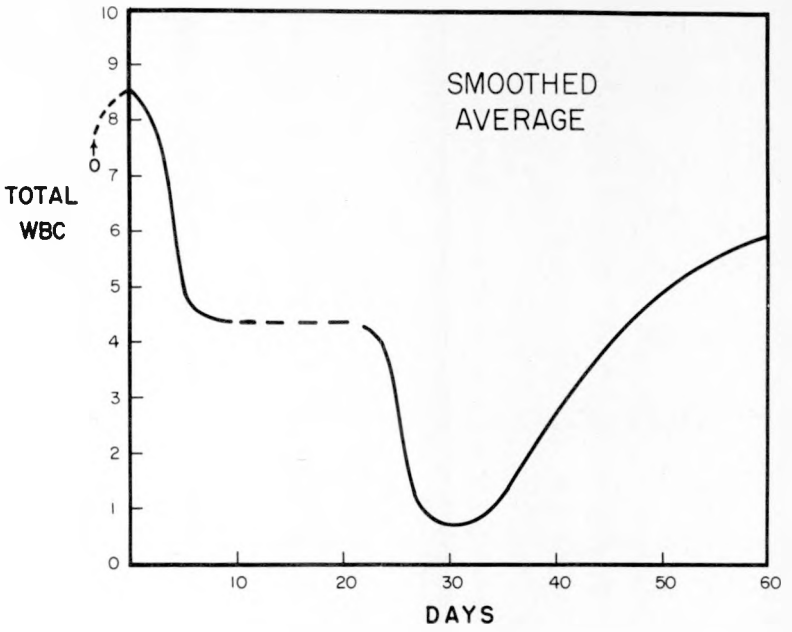

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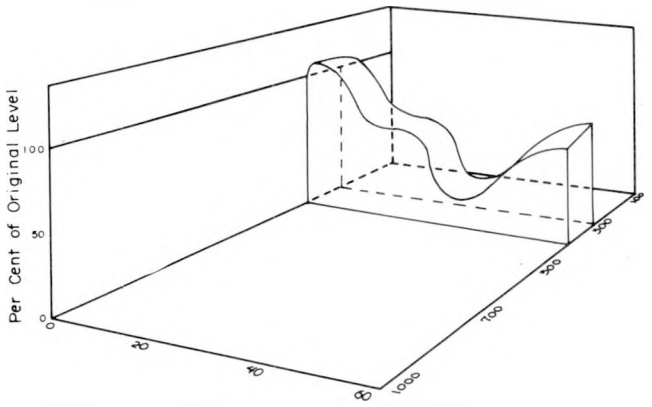

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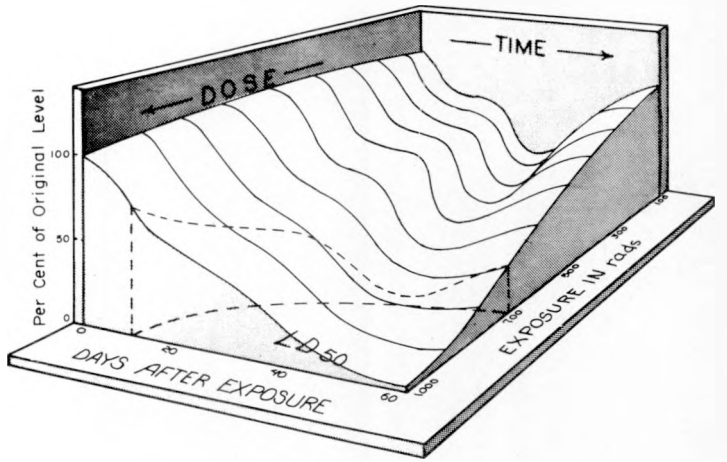

MAKING A 3-DIMENSIONAL CHART

irradiation exposure, we have taken the actual data from five patients. These data have then been smoothed out to form our impression of a generalization of what probably would happen in future patients at this level. This level is only one of many levels that might be of interest, and so this was then extrapolated to all the other levels of interest. It should be remembered that for most of these other levels no data are available. We have only hints from widely varying sources. As shown in the illustration, this was then extrapolated to a smooth generalization over an entire range of interest.

All the following charts are in three dimensions. One dimension is the dose received by the patient. The second is the time in days after the accident; neither variable is sufficiently constant or predictable to describe in terms of accurate units. Therefore, the charts are drawn purposely so that they cannot be read as definitive data. These are impressions only. The third axis on the three-dimensional graph is the variable under discussion. An arbitrary 100 per cent is taken as the height of the chart; on some graphs this 100 per cent means the incidence of the event. On others it means the effective clinical impression; on still others it refers to a definite measurement. On the other hand, the level of the Z axis on any of the three-dimensional surfaces can not be considered more than an approximation.

Description of the Accident. The Y-12 accident occurred in the early afternoon of June 16, 1958.* An employee of the Union Carbide Nuclear Company was filling a 55 gallon drum with clear (?) water in order to dissolve a residue of enriched uranium. This is a normal procedure in the uranium-recovery operation. The same operation had been done many times before by this particular employee and always with complete safety. On this particular occasion, however, there was a sufficient amount of enriched uranium so that as the water was added, a geometric configuration was reached that allowed the enriched uranium to reach a critical level and the drum began to act as a reactor. As it reacted the power level increased, the amount of heat produced increased, and the volume of water quickly began to "boil." However, the boiling destroyed the necessary geometrical configuration for criticality. The reaction ceased, and it stopped boiling. As it cooled off a critical conformation was again reached. The drum again went critical causing it again to boil and to automatically shut itself off. This oscillation was repeated every few seconds. Both neutrons and gamma rays were produced and the fission products resulted in a continuous build-up of gamma-ray intensity. Since water was constantly flowing into the container, it soon diluted the material beyond that required

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* Accidental Radiation Excursion at the Y-12 Plant. U.S. Atomic Energy Commission Report Y-1234, July 28, 1958, 77 pp. with appendices and illustrations. Available from the Office of Technical Services, Department of Commerce, Washington 25, D. C. Price $2.75

for a critical reaction.

Shortly after the first gamma rays were produced the radiation alarm sounded. The employee who was filling the container with water was standing a few feet from the drum alternately watching a meter and the filling process. Two employees were repairing a duct about 20 feet from the source of activity. Two other employees were repairing a pipe about 15 feet from the source of activity. In both pairs of workers, one of the men was standing on the floor, and the other was mounted on a ladder. One of the employees was much higher on his ladder than the other one was on his. The employee filling the drum noticed a blue flash and a yellow haze, heard the alarm and probably was the first to leave the area. Two of the other employees saw a blue glow but this may have been a reflection. They noticed a haze throughout the area, heard the alarm, and left, but not quite so rapidly as the first man.

Three other employees were in the area but at a considerable distance from the source of activity. The doses they received were probably in the 20 to 60 rad range; they had no signs or symptoms of radiation effects and are no longer considered in this report; no other persons received significant dosage. The five men who were closest to the accident had a dosimetry that is summarized in section one of this report. In general, it appears that the biological dose to these patients was in an order of magnitude greater than that described in Case 5 in the Los Alamos report, but less than that described in Case 4 of the Los Alamos report.

Twelve Clinical Factors

The three-dimensional charts that follow are based not only on our own experience with the Y-12 accident victims, but on the experience of Cronkite and Bond in the Marshallese incident, Hempelmann in the Los Alamos incident, and Gerstner's review of all known accidents. From these experiences and the results reported in the literature, it is possible to get a general impression of what happens after radiation accidents in man. The many animal studies on radiation effects also give many hints at what might happen. Even so there is still insufficient experience to give more than the most general kind of summary data. The following references were helpful in caring for the patients:

Brucer, M. Future Accidents in Oak Ridge: Plans for Medical Care. Mimeographed. Distribution to AEC.

Cronkite, E. P., Bond, V. P. and Dunham, C. L., editors. Some Effects of Ionizing Radiation on Human Beings. A report on the Marshallese and Americans accidentally exposed to radiation from fallout and a discussion of radiation injury in the human being. USAEC Report, TID-5358, July 1956.

Gerstner, Herbert B. Military and Civil Defense Aspects of the Acute Radiation Syndrome in Man. School of Aviation Medicine, USAF, Randolph AFB, Texas, 58-6, November 1957.

Guskova, A. K. and Baisogolov, G. D. Two Cases of Acute Radiation Disease in Man, in Proceedings of the International Conference on the Peaceful Uses of Atomic Energy. Vol. 11, United Nations, New York, 1956, pp. 35-44. (Original language: Russian.)

Hasterlik, R. J. and Marinelli, L. D. Physical Dosimetry and Clinical Observations on Four Human Beings Involved in an Accidental Critical Assembly Excursion, in Proceedings of the International Conference on the Peaceful Uses of Atomic Energy. Vol. 11, United Nations, New York, 1956, pp. 25-34. (From the Argonne Cancer Research Hospital, Chicago, and the Argonne National Laboratory.)

Hayes, Daniel F. A Summary of Accidents and Incidents Involving Radiation in Atomic Energy Activities, June 1945 through December 1955. USAEC Report, TID-5360, August 1956.

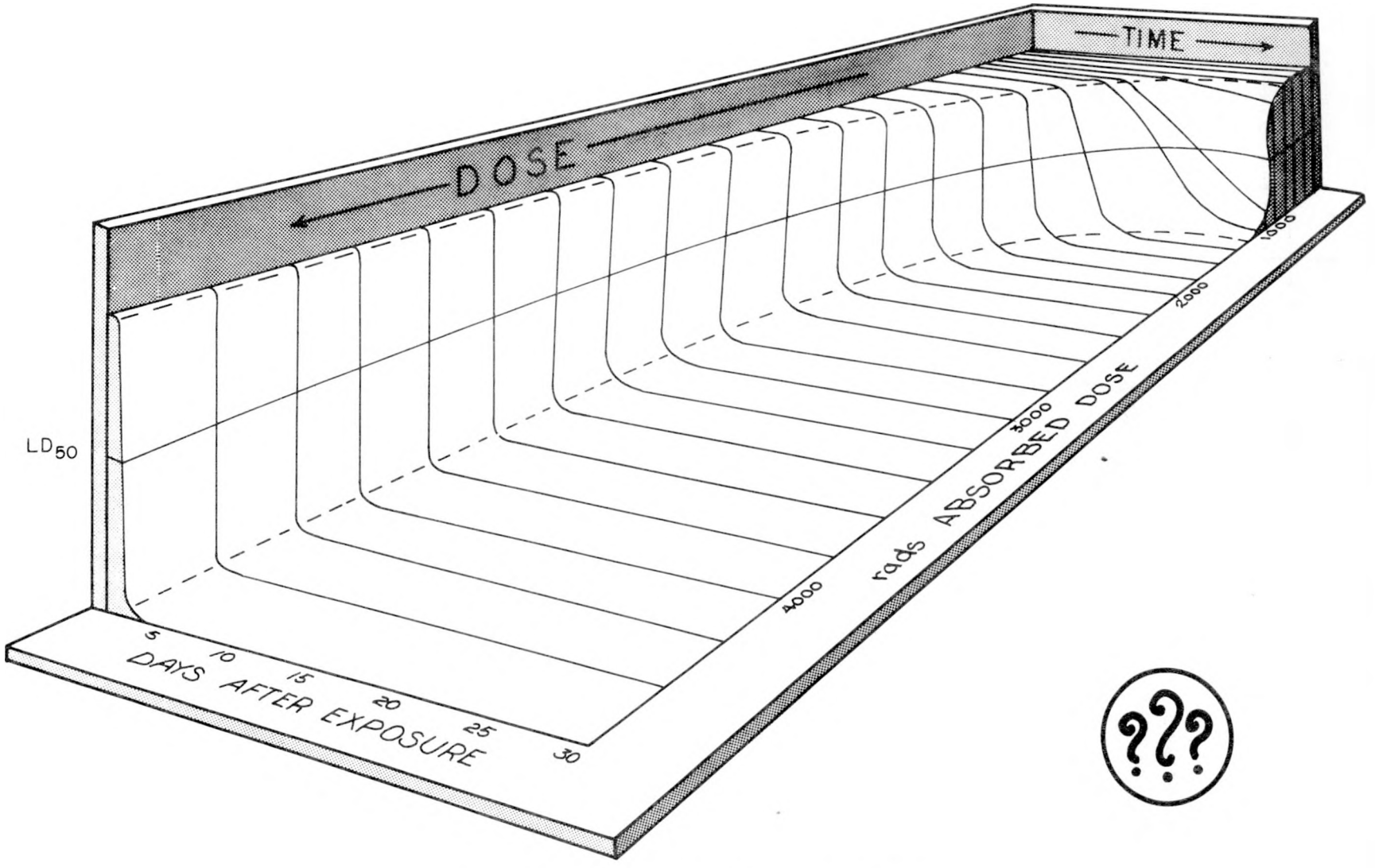
Hempelmann, L. H., Lisco, H., and Hoffman, J. G. The Acute Radiation Syndrome: A Study of Nine Cases and a Review of the Problem. Ann. Int. Med. 36, 279-510, 1952.

Hempelmann, L. H. and Lisco, H., compilers. The Acute Radiation Syndrome. A Study of Ten Cases and a Review of the Problem. Los Alamos Scientific Laboratory, LA-1095, LA-1096, and LA-1097 (Volumes I, II, and III) March 17, 1950.

Sinclair, W. K. and Cole, A. Technic and Dosimetry for Whole-Body X-Irradiation of Patients. School of Aviation Medicine, USAF, 57-70, March 1957.

A Summary of Transportation Incidents in Atomic Energy Activities, 1949-1956. AECU-3613, December 1957.

THE ACUTE RADIATION SYNDROME IN MAN



THE LETHAL DOSE

1. Dosimetry in Total-Body Irradiation

The dosimetry of radiation has a long and distinguished history. Unfortunately, most of this history was built around either the physical measurement of radiation (which is exceedingly important but not pertinent to this discussion); or it was built around partial-body therapeutic irradiation (which is a highly controlled method of radiation based upon much experience and yielding a different postirradiation picture from that of total-body irradiation); or it is centered around exceedingly small doses of radiation (which are not pertinent to this discussion).

When we look at the whole picture of total-body irradiation (Fig. 1c) from no dose to many thousands of rads of absorbed dose, a picture that is probably correct appears to be emerging. If we consider only the first 30 days following the total-body irradiation, and very small doses, no immediate medical effects appear to be present. If doses of the order of 5000 rads are received, data appear to be similar to those of the irradiation of large animals. The patient gets severely sick within minutes and dies within hours as in the 1958 Los Alamos case. From these scanty data apparently this change from death in many hours to death in many days is a change from lethal to superlethal levels of radiation absorption within a few hundred rads at about the 1000 rad level. This superlethal exposure level is of intense interest to pathologists but probably is not of immediate interest to practicing physicians. Little to help the patient can be done in this area.

In Fig. 1c it appears reasonable to assume that an area of immediate interest to physicians lies between the 100- and 1000-rad levels. Above this level we are helpless and under this level we are unnecessary. (The chronic effect is a different story.)

LD-50 - A Most Probable Guess and the Acceptable Guess (Figs. 1a and 1).* Two LD-50 charts are presented in the range of greatest clinical interest. The first one, Fig. 1a, is the lethal dose that can probably best be expected from a combination of animal studies and human studies. The second estimate, Fig. 1, is the picture that probably should be remembered by physicians who have to take care of patients. The reason for the double presentation is that we have insufficient evidence to make a decision. If we follow the hints we have had from very extensive animal work, then it would appear that man, like every other biological animal, has a very sharp response (by acute lethality) to radiation. It would seem from total-body-irradiation studies on very few patients that levels of exposure of around 600 r probably lead to few, if any, acute radiation deaths. Levels of more than 1000 r probably always lead to acute radiation deaths. This very rapid transition

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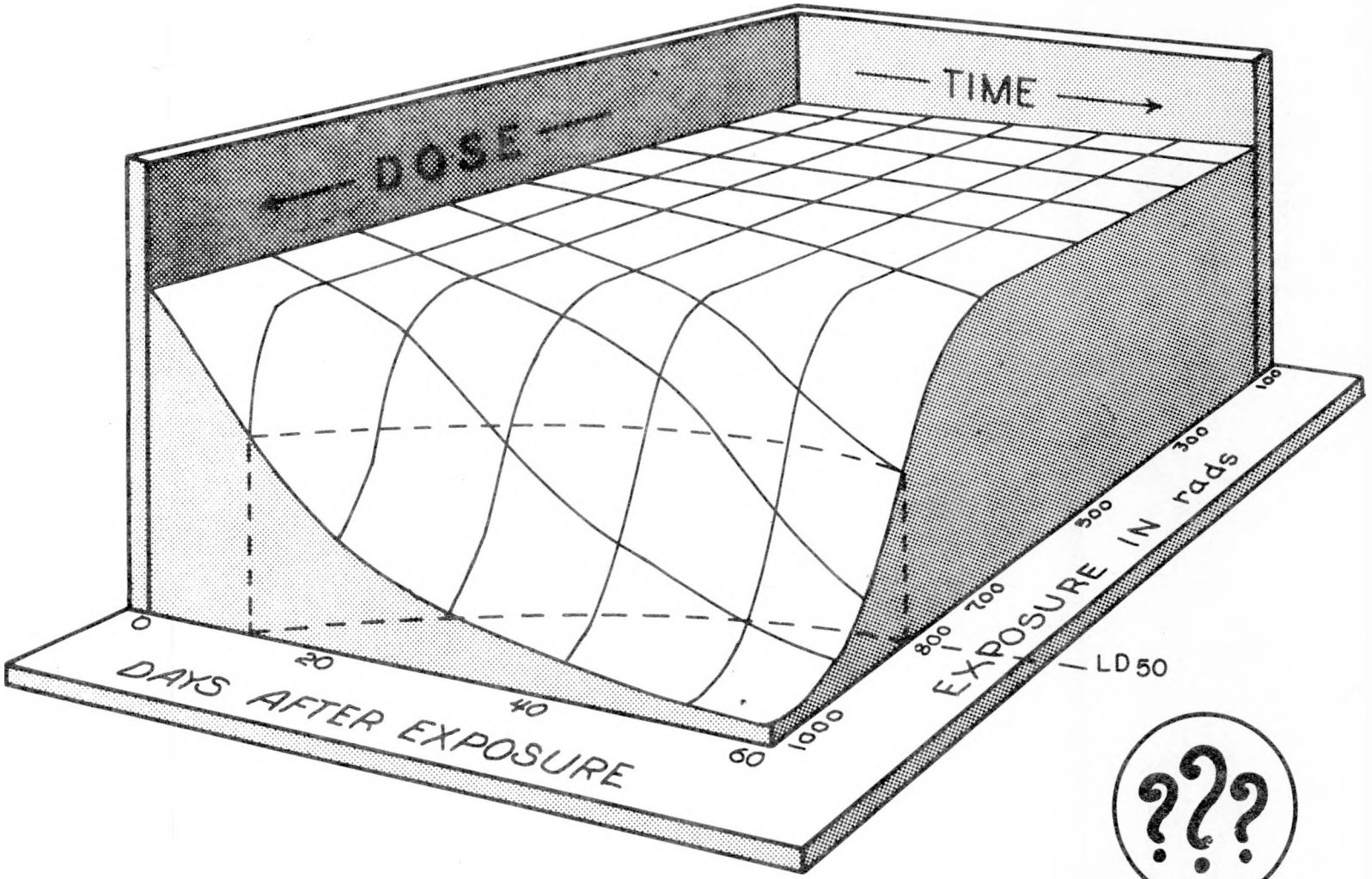
* Fig. 1b was a temporary chart that has been deleted because it did not contribute additional information.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN



GUESS AT ACTUAL LETHALITY

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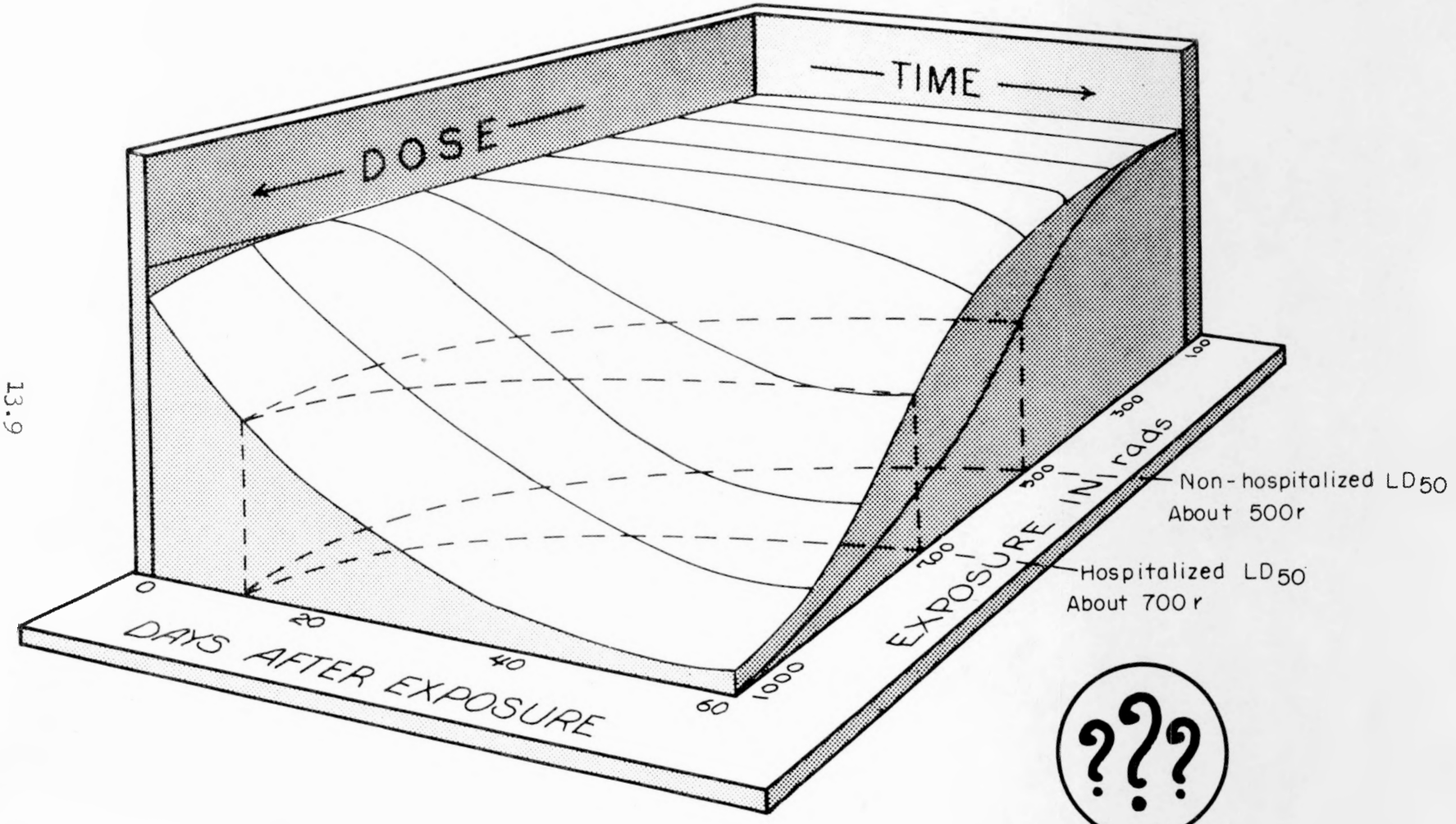
12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

(1)



LD 50

(within an exposure of a few hundred roentgens) from an LD-0 to an LD-100 is in keeping with most animal studies. Fifty per cent of humans will die within about 60 days no matter what is done when the radiation exposure is at about the 800 r level.

In the absence of better estimates, however, it is probably unwise for a physician to base his therapy on such a sharp distinction between nonlethal and lethal doses. Many serious radiation accidents may occur within this range.

In a civil defense situation, when thousands of patients are submitted for immediate medical care, it might be necessary to keep in mind the most probable lethal dose ranges. However, in an industrial situation where there is plenty of time, effort, and money available to take care of each patient as an individual, the 200- or 300-r range to the 600- or 700-r range of exposure must be considered as an exceedingly dangerous range. It is in this range where medical therapy can be of greatest value. In this industrial situation it would be unfortunate for physicians to give up in the 800 to 1200 r range merely because animal studies indicate that the exposure might be overwhelming.

The unit of measurement on the dose axis probably should be given in arbitrary units. I am using the rad instead of the rem for the following reasons. The rad is internationally accepted, precisely defined, and has a meaning that is probably fundamental to all biological studies. The rem was originally devised as a health physics unit and in the words of its originator, Dr. Robert Stone, is a "unit of convenience." Health physicists use it because they are responsible for personnel exposed to neutrons along with gamma and X-rays. They need a unit for protection measurements to include all kinds of ionizing radiation. The rem is an attempt to combine some dose figure with a Relative Biological Effectiveness (RBE), which is a compounded inaccuracy. For example, at the time of the Oak Ridge accident, four of the physicians responsible for the clinical care of the patients interpreted the stated rem unit in four different ways. After the first few days the clinicians dropped the rem and used the rad. It is prudent for a physician to use a unit that has an international acceptability.

Nevertheless, even though the rad meets the requirement that it is internationally acceptable and understood, it has many faults. In the first place, we have no convenient rad calibration for mixed-neutron irradiation. In the second place, we have no certain gamma spectrum in any accident, or even a good estimate of the gamma exposure. None of the health physics instruments (film badges, pocket dosimeters, or area monitoring devices) or any of the units in which they can be physically calibrated are really satisfactory in a mixed neutron-beta-gamma dosimetry. In a wide spectrum of energies, such as probably must be expected in most reactor accidents, none of the units used have any really fundamental meaning. Nevertheless, one of the lessons I believe we have learned from the accidents that have so far occurred is that all

dose units should be given in rads. The physician can apply his own correction factors for the neutron dose.

In the logistics of medical care and in the prognosis of the therapy that will probably be necessary, the physician must keep in mind the dose level that is likely to be lethal. Usually in most animal experiments this is stated as an LD-50 dose. Although the LD-50 dose is an important concept in experimental biology, it is an unreasonable and unrealistic concept in the treatment of patients. Nevertheless, it is useful to have one number to use as a guidepost, provided the physician realizes that LD-50 is only a guidepost.

In our experience with the treatment of leukemia patients with total-body irradiation, it is already apparent that the commonly stated LD-50 of 450 r is probably too low.* It appears that this misinterpretation is due primarily to the fact that in most animal experiments and in the original Japanese atom-bomb studies, a prolonged period of care in a hospital was not immediately available. It might be that the 30-day LD-50 for patients not admitted to a hospital is lower than that for patients who are given rudimentary medical care.

In patients who receive adequate hospital care immediately after a radiation exposure, the LD-50 appears to be around 800 rads for the 30- to 60-day time limits. When the dose is much higher, more than 1000 rads, death certainly occurs much earlier and the course of the disease appears to be much more severe. In this range, death seems to occur in about the same dose-time relationships as in the patients without hospital care. In future discussions of LD-50 in humans it will be necessary to take into account the postirradiation treatment of the patient. Hospital and medical care are most effective in the ranges of more than a few hundred rads and are probably ineffective in ranges of more than 1000 rads. For an exposure of only a few hundred rads, medical care is certainly psychologically supportive and might easily be of value even after the acute phase has passed. In the range of more than 1000 rads, medical care is humanitarian and as such has its own importance.

When the words "low-dose range," "medium-dose range," and "high-dose range" are used in health physics, they have an entirely different meaning from our use in discussion of radiation accidents. For the purpose of this document, I am giving the words a well-defined meaning. By "low-dose range" I mean doses in the range between almost a hundred to a few hundred rads. This is the dose in which we can reasonably expect no acute lethality and only a relatively minor radiation sickness that is treatable with sedation alone. The "medium-dose range" means the range of exposures from a few hundred rads to slightly over a

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* V. P. Bond of Brookhaven disagrees strongly and thinks that the LD-50 is less than 450 r; however, I think he is talking about LD-0 and not LD-50.

thousand rads. This is the range of radiation dose in which the acute lethality is progressively worse. It is the range in which heroic medical therapy is not only justifiable but might often be of tremendous value. By "high-dose range" I mean doses of much more than 1000 rads in which the therapy is only supportive and humanitarian.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

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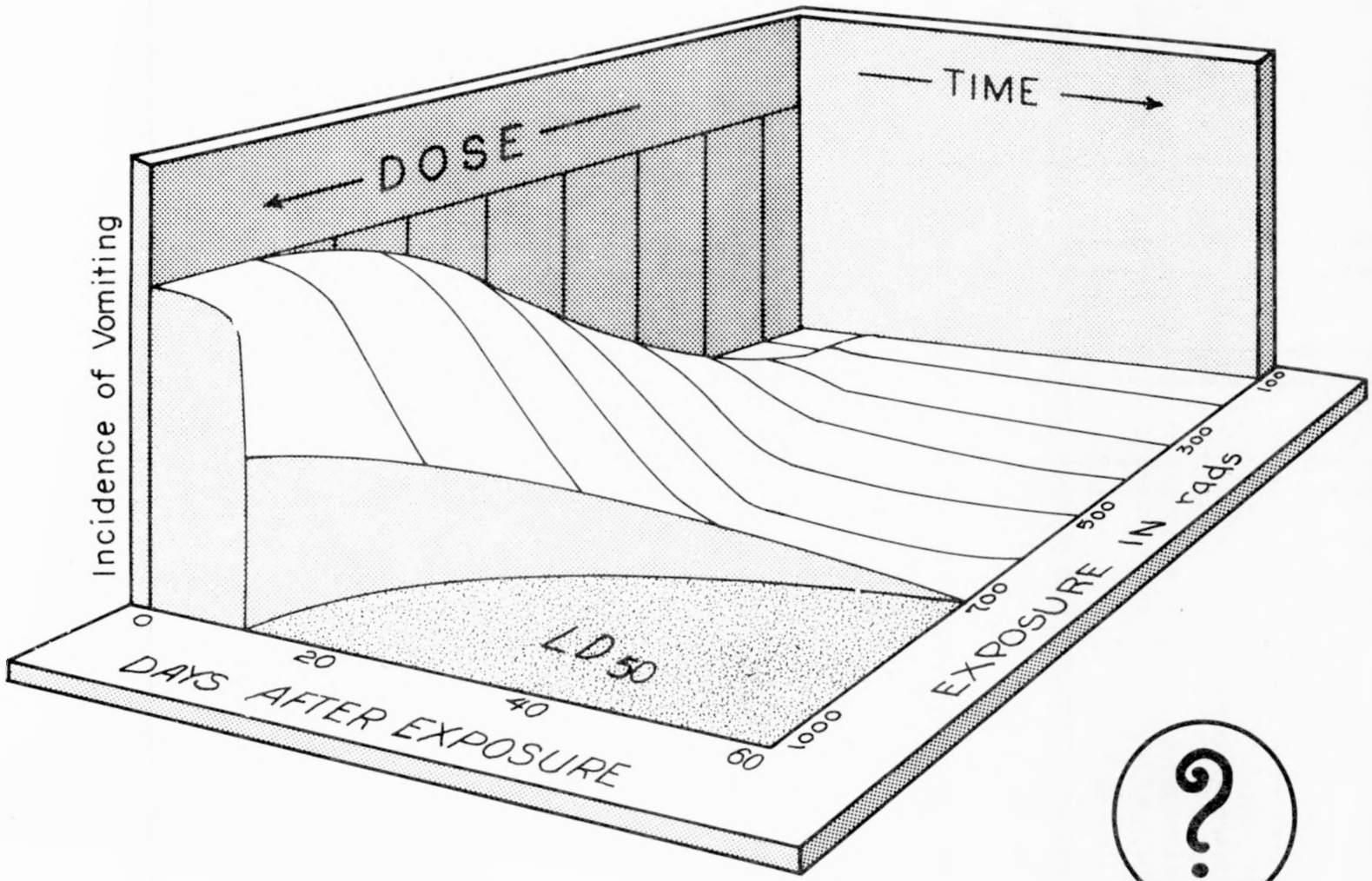

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VOMITING

ORINS - MB - 59

2. Vomiting

Probably the only clinical sign that will give the physician any hint of the level of radiation is the nausea and vomiting that occurs shortly after exposure to radiation. When the dose is less than 100 rads, there is seldom any indication of nausea and vomiting, and this (when present) occurs late. At very high doses, nausea and vomiting occur frequently and early. The relationship of the incidence of vomiting, and the degree of intensity of vomiting and nausea does not appear to be a linear one. It appears that at about 200 to 400 rads the increase in both incidence and severity is rapid. With more than 800 rads incidence of nausea and vomiting is always high and severe.

Nevertheless, vomiting is not a clinical sign that can be trusted beyond good clinical judgment. The psychological effects of a severe scare can in themselves cause vomiting. There are occasional reports of vomiting at very low doses. When high-dose and low-dose patients are mixed in the same ward room there is a good possibility that much of the vomiting in low-dose patients might be psychogenic. The publicity on radiation accidents has been sufficient to instruct people that they should vomit. Complicating trauma and ugly-looking wounds can themselves cause vomiting. Vomiting is a sign that must be interpreted with cagey clinical judgment.

In the medium-dose range vomiting is a clinical sign that is treatable. The physiological effects of vomiting probably should not be treated until definitely indicated.

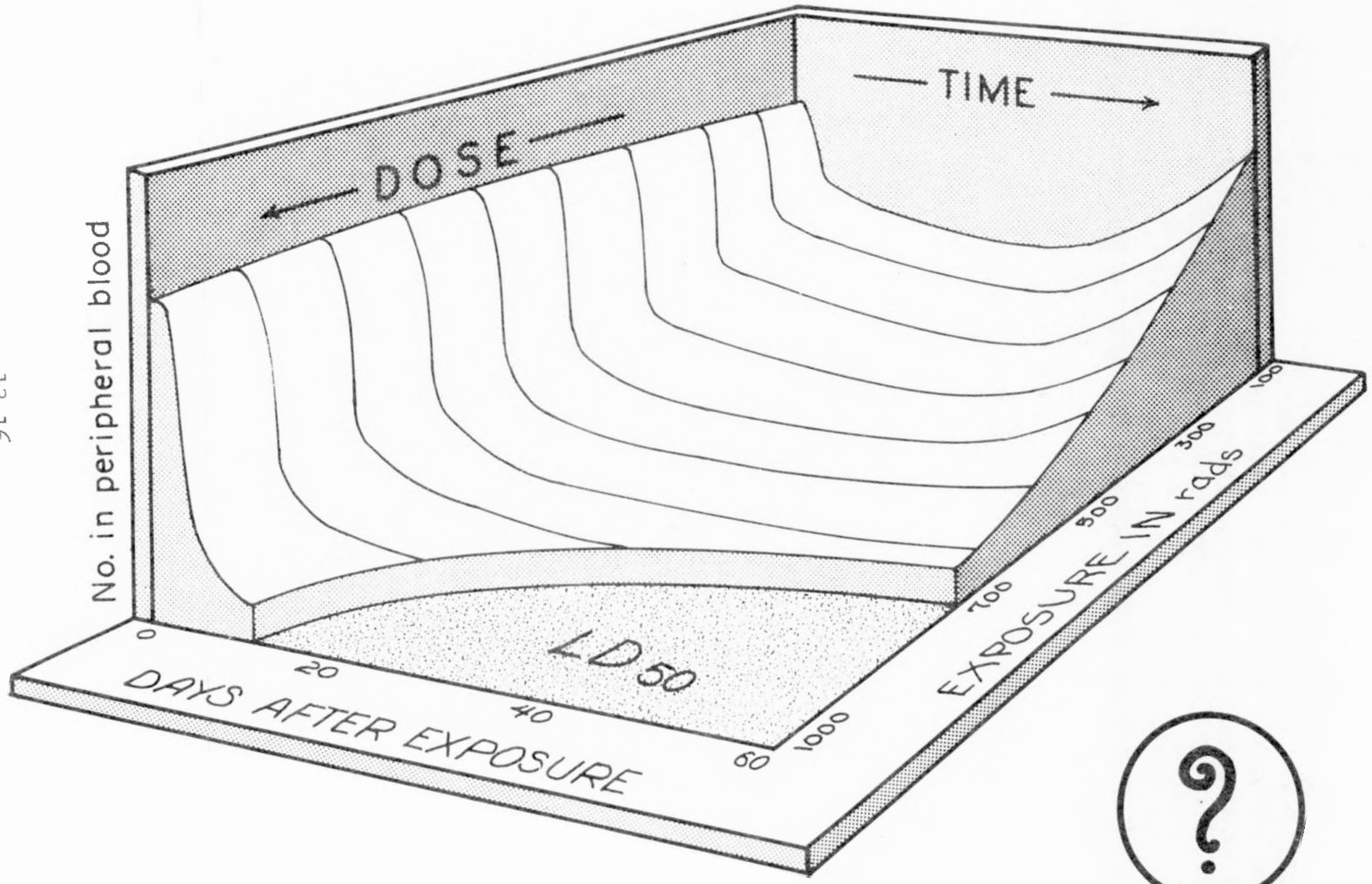
It would appear that none of the vomiting that occurs after several days, in patients who have received a reasonably large dose of irradiation, is due to the radiation itself but to complications of various kinds. Apparently true radiation vomiting disappears after the first week and does not appear again. Diarrhea does not appear to be a part of the sublethal external irradiation picture, but it is reported in connection with internal contamination. At very high doses diarrhea may be a part of the symptomatology.

In general, prolonged, severe, and early vomiting is a serious clinical sign. It probably indicates that the patient received a high dose of radiation. Incidental, late, and infrequent vomiting is probably a sign of low dosage.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

3



LYMPHOCYTES

3. Lymphocytes

A decrease in lymphocytes in the peripheral blood probably means nothing more than that the patient has been exposed to a significant amount of radiation. Soon (hours) after a radiation exposure, all patients seem to show a significant decrease in the lymphocyte count. The degree of depression shows up only a few days later and here the depression appears to be dose related. At very low doses, the depression in lymphocyte count occurs rapidly, stabilizes at a reasonably high level but does not return to normal until after many weeks have passed. In very high doses the lymphocyte count is depressed to a greater extent, stabilizes, and slowly climbs back to normal after many months.

Therefore, the lymphocyte count by itself does not give much useful information in the first few hours after a radiation accident. If the depression does not go down to very low levels during the first few days after the accident, it probably means that the dose of radiation was not in a lethal range. Still, the depth of depression after the first few days is not a good sign that the patient is or is not in the LD-50 range. An increasing lymphocyte count after the first week probably is an exceptionally good prognostic sign.

Dr. Thomas Shipman of the Los Alamos Scientific Laboratory feels somewhat different about the lymphocyte count. He believes from evidence on a small number of severe radiation accidents in Los Alamos that of all the laboratory tests, the total lymphocyte count, followed over a period of 24 or 48 hours, is the most sensitive indicator. In a very preliminary way he gives a specific statement that he tends to follow: a count that goes to 500 or less in the first 24 or 48 hours certainly indicates a grave prognosis; if the count remains above 1000, Dr. Shipman feels that he can be reasonably optimistic. Although this distinction is certainly true in separating the high-dose from the medium- or low-dose patients, it is probably not completely true within the range of medium-dose patients.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

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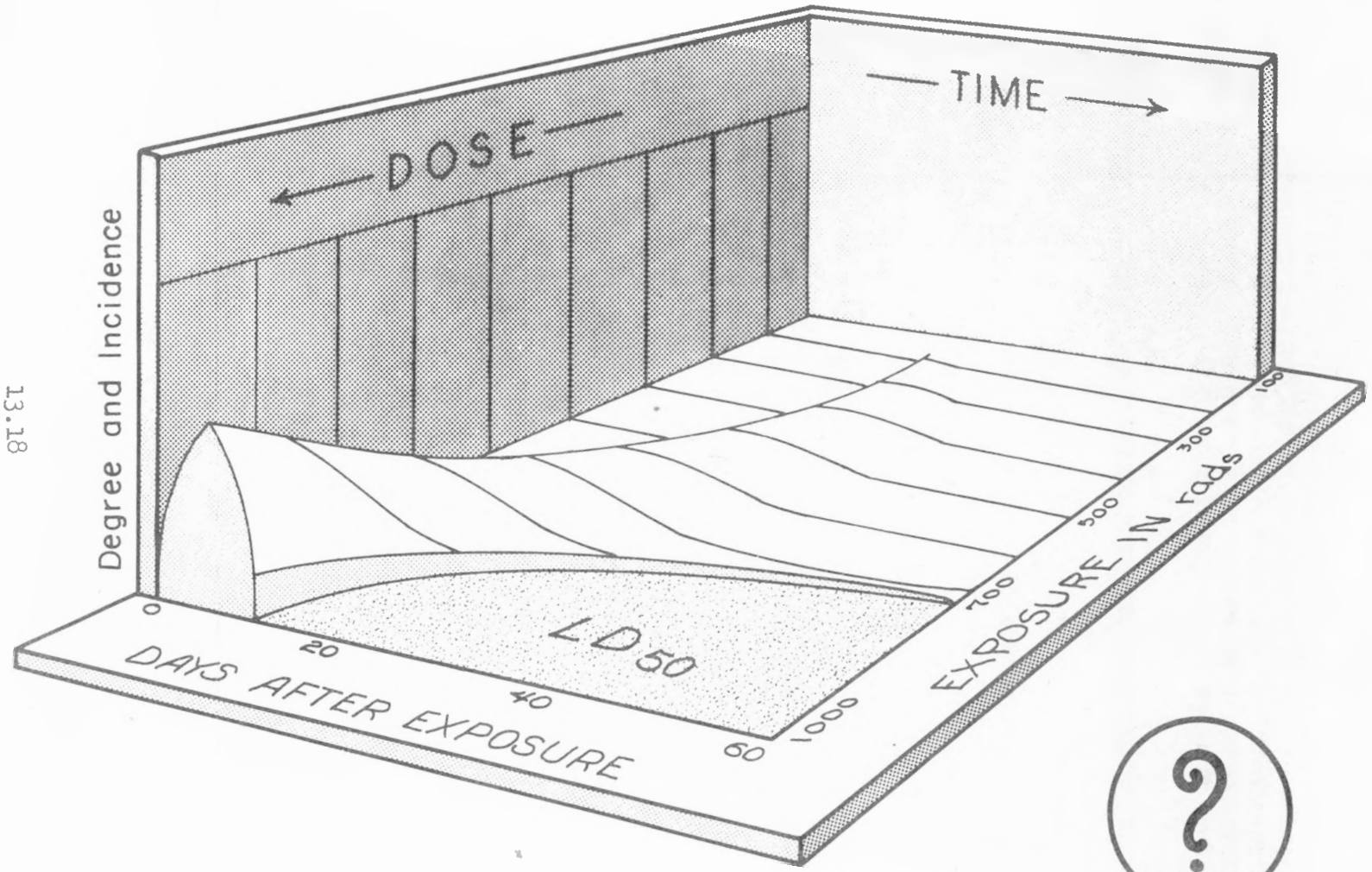

ERYTHEMA

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4. Erythema

Erythema is more closely related to "energy" than to "amount" of radiation. A fairly large dose of low-energy radiation will produce erythema without producing any other symptoms. A large dose of high-energy radiation may produce the same erythema. The association of some skin contamination, particularly with beta-ray emitters, may produce erythema that has very little effect on the total-body dose. It is a confusing sign to look at unless all the physical factors concerning the accident are known.

In general, with doses in the low range, erythema is late and is of no special significance. When the erythema appears early it means that the dose has been high. The distribution of erythema on the body may or may not have a relation to the position of the patient in respect to the source of activity. Photons scattered from high-energy gamma radiation are more likely to produce erythema than is direct high-energy radiation; therefore, the erythema may appear on positions of the body that are more related to surroundings than to the direction of the source of activity. With very high-energy radiation the exit dose may be higher than the entrance dose in the body, and erythema could appear opposite the direction of the source. Thermal neutrons are less penetrating than slow neutrons, and slow neutrons are less penetrating than high-energy neutrons. The same is true but to a different degree of all kinds of radiation.

The physician who sees only erythema and knows nothing else about the patient might be looking at a patient who was out in the sun the day before, or he might be looking at a very high-dose patient. Although erythema is a hazardous sign to base clinical judgments upon, it probably means that the patient has been exposed to a very high dose of radiation if it is combined with severe vomiting and nausea and with a picture of decreasing lymphocyte count. Prophylactic treatment should then be given. When there is a drop in lymphocytes, little vomiting and nausea, and no erythema, the syndrome probably means that the patient has not been exposed to a high dose of radiation. Before making any attempt to interpret erythema, the physician should find out all he can about the spectrum of energies and the kind of radiation to which the patient was exposed. It must be remembered that during the first hours after the exposure, much of the essential information concerning the physical details of exposure is liable to great error. This is not necessarily the fault of the health physicist who has troubles of his own.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

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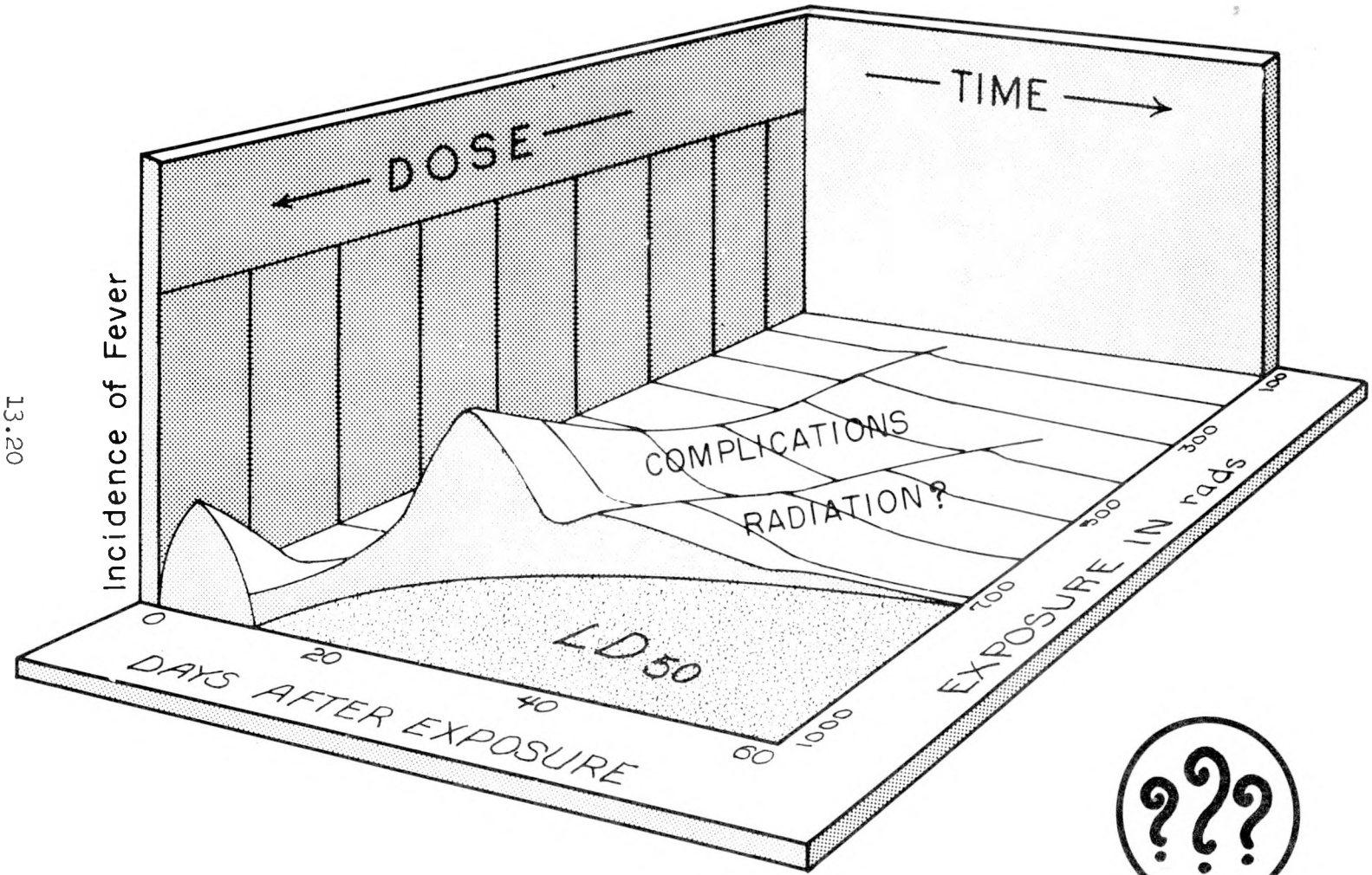

BODY TEMPERATURE

13.20

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5. Body Temperature

The observation of fever in a patient who has been exposed to radiation might be an exceedingly bad sign. A fever that occurs early has been described only in a very high dose of radiation. This was in the superlethal range. The fever due to radiation exposure in the lethal and sublethal range usually occurs late and is not particularly informative. Superimposed on the three-dimensional surface that describes radiation-induced fever is fever that is due to complications of radiation accidents.

Within a few days after a significant dose of radiation, it seems that patients are unusually susceptible to infection. This has been hinted at in almost all the human and animal studies. It is prominent in the Russian literature. It is easy to explain on the basis of brain damage, but it is difficult to interpret a fever (as radiation induced) that appears a few hours after a radiation accident except in terms of superlethal dosimetry. The fever that appears in the first few days after the accident is very likely to be due to a complication and sources of infection should be looked for.

Patients that live through a moderate dose of radiation may go through a peak of fever. This is why some texts recommend prophylactic antibiotics. In the lower dose ranges the fever is primarily due to complications and has no diagnostic significance concerning the radiation dose. It must be treated, but as an infection, not as radiation damage. A later peak of fever may appear in the patients that live through the lethal phase; this peak may have some relation to the radiation itself, but usually this is of little significance in the treatment or prognosis of a patient. Dr. Cronkite of Brookhaven feels that there is not one shred of evidence for a radiation-induced fever (except maybe in very high doses). I agree but am impressed by the Russian literature.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

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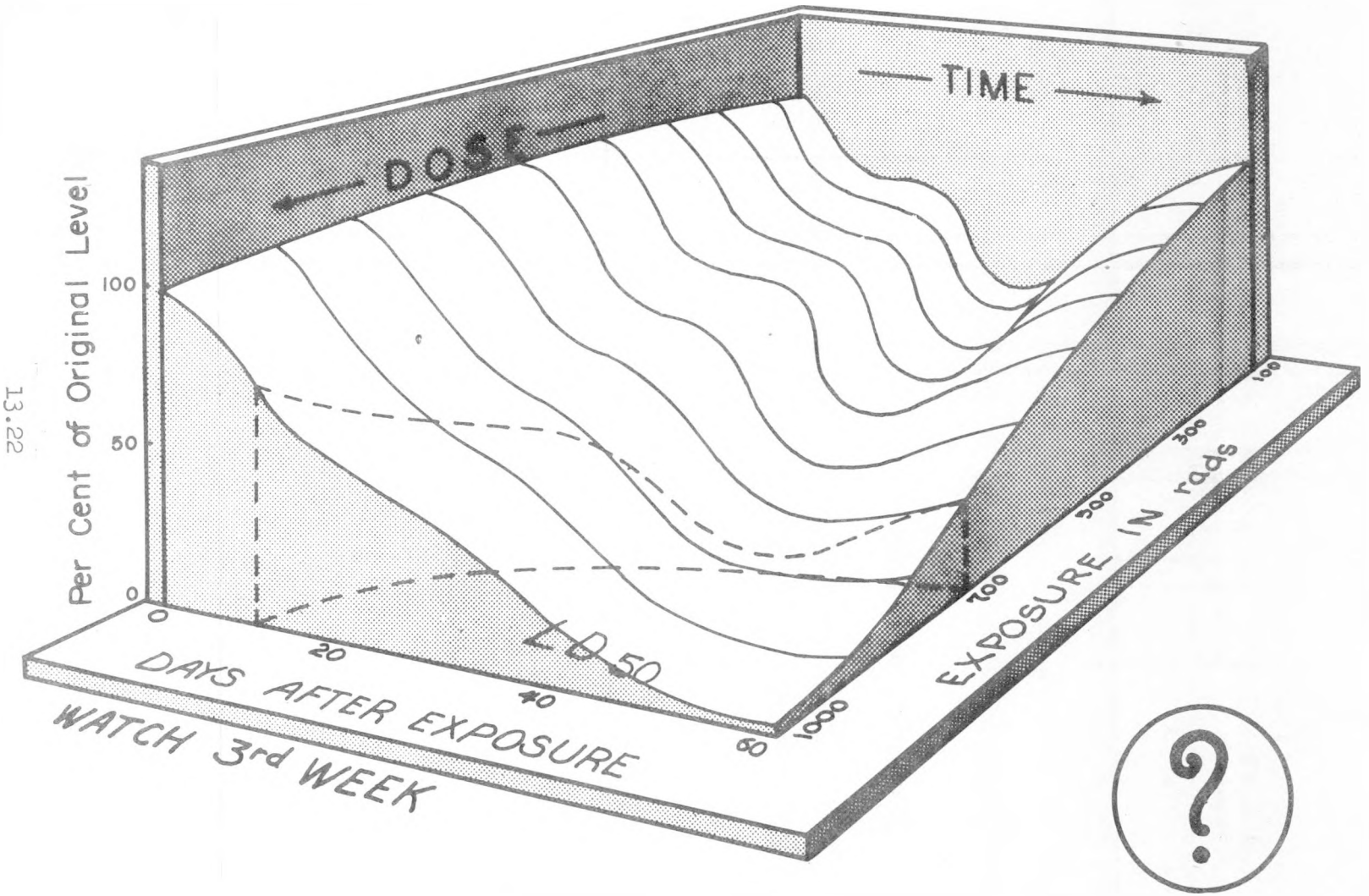

TOTAL WBC

13.22

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6. The Total White Blood Cell Count

Hematologic details are among the best known laboratory signs of radiation damage. It is expected that in any severe radiation accident a hematologist would be called in to do special bone-marrow studies, serial differential counts, thymidine uptakes, mitotic indices, platelet counts, and other specific studies that are a part of a good hematology review. In this series of charts, however, we are mentioning only the things that can be done by a relatively unspecialized physician without special research laboratories to back up his opinion. So far as we know, except for the detailed hematology studies, there are no special laboratory procedures (as yet*) that are of exceptional diagnostic or prognostic significance in following the patients. Only in reference to hematology studies will it be necessary for the usual internist, pathologist, or general practitioner to call for specialized help. Lymphocyte and neutrophil counts, ordinary platelet counts, and the appearance of bleeding are available to any clinical pathology laboratory and hence they are included in this survey.

There is an impression among hematologists who have studied radiation accident cases that there is probably a mild increase in the total neutrophil count immediately after a radiation accident. This increase in neutrophils is usually not of diagnostic nor prognostic significance because there will usually be no base line of normal white blood cell levels in patients from industrial accidents. Also this mild initial increase in neutrophils appears to occur in both low and high doses; even if it were possible to accurately assess the degree of neutrophil increase, it would probably not be of diagnostic significance.

After the first few days the white cell count invariably decreases; this decrease appears to be rapid and alarming for about a week. This is a period in which observers have noticed great fluctuations, or a leveling off of the decrease, which might be interpreted as the beginning of regeneration. This leveling off probably represents a mobilization of white cells into the peripheral blood and usually is without any significance except that it might give the impression that the period of neutrophil decline has ended. This is not always true because the neutrophil count continues to decrease at a somewhat alarming rate until extremely low levels are achieved after three to five weeks have passed. Recovery to normal levels may take many months even in patients who have received only 100 to 200 rads.

On hindsight it is possible to look back and see that, in low doses (100 rads) of radiation, the depression of white cell count is

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* Recent amino acid studies on the urine and blood may soon change this statement. There appears to be an increase in taurine, a disappearance of serine, and an increase in beta aminoisobutyric acid.

not so severe as in the higher-dose patients. Even so, while this is occurring, the degree of depression does not assist the physician very much in prognosticating the course of events. The fluctuation in white cell count that might occur fairly early after radiation may or may not be related to an infection superimposed on radiation.

When the white cell count is correlated with other data, then it does seem to have some diagnostic significance. If there has been very little vomiting, no erythema, and the lymphocytes are not too greatly depressed, then the prognosis is probably good and the depression of the white cell count indicates only a natural course of the disease. An increased white cell count along with an early fever probably is significant of a superimposed complicating infection. A violent fever without an increase in white cell count probably demands a careful search for a source of infection and the immediate administration of antibiotics. There is probably an even greater demand for the search for infection if the fever is not accompanied by an increased white cell count. The normal hematologic aids to diagnosis tend to be reversed after acute irradiation.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

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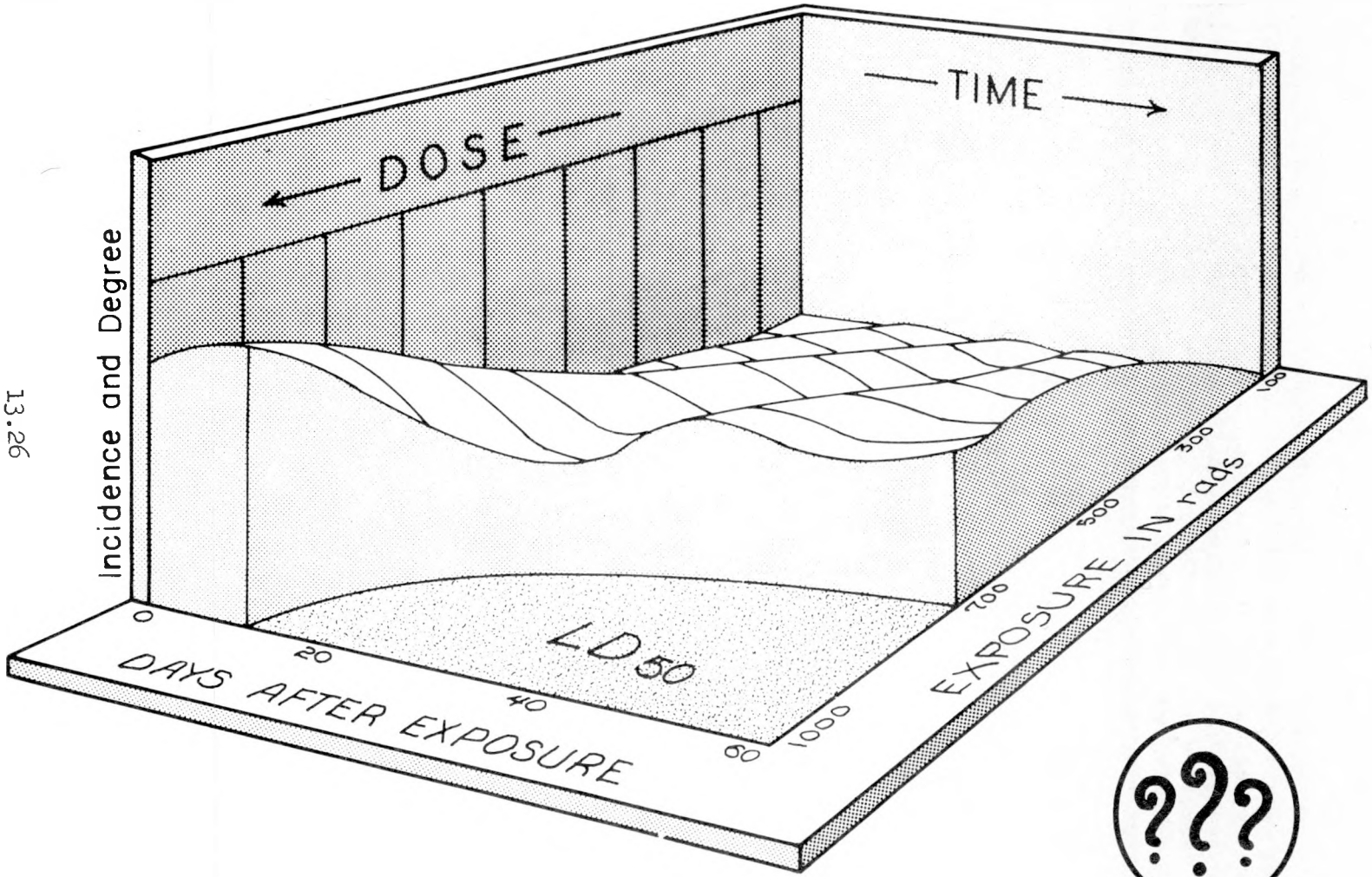

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FATIGUE

13.26

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7. Fatigue

One of the most important clinical symptoms after severe radiation damage is fatigue. It is a symptom that is difficult to describe and impossible to quantitate, but is obvious to an astute clinician. The people who have watched irradiated monkeys have noticed this symptom, but since it is so subjective, they have been unable to quantitate it. The impression the observer gets of low-dose fatigue in the monkey is blended in with a meningismus and hyperexcitability that appear at higher doses. When humans are treated with large doses of radiation, these are usually patients having another illness that obscures the picture. In radiation accident victims an initial wave of fatigue is invariably followed by a period of well-being, which may again be followed by a wave of fatigue.

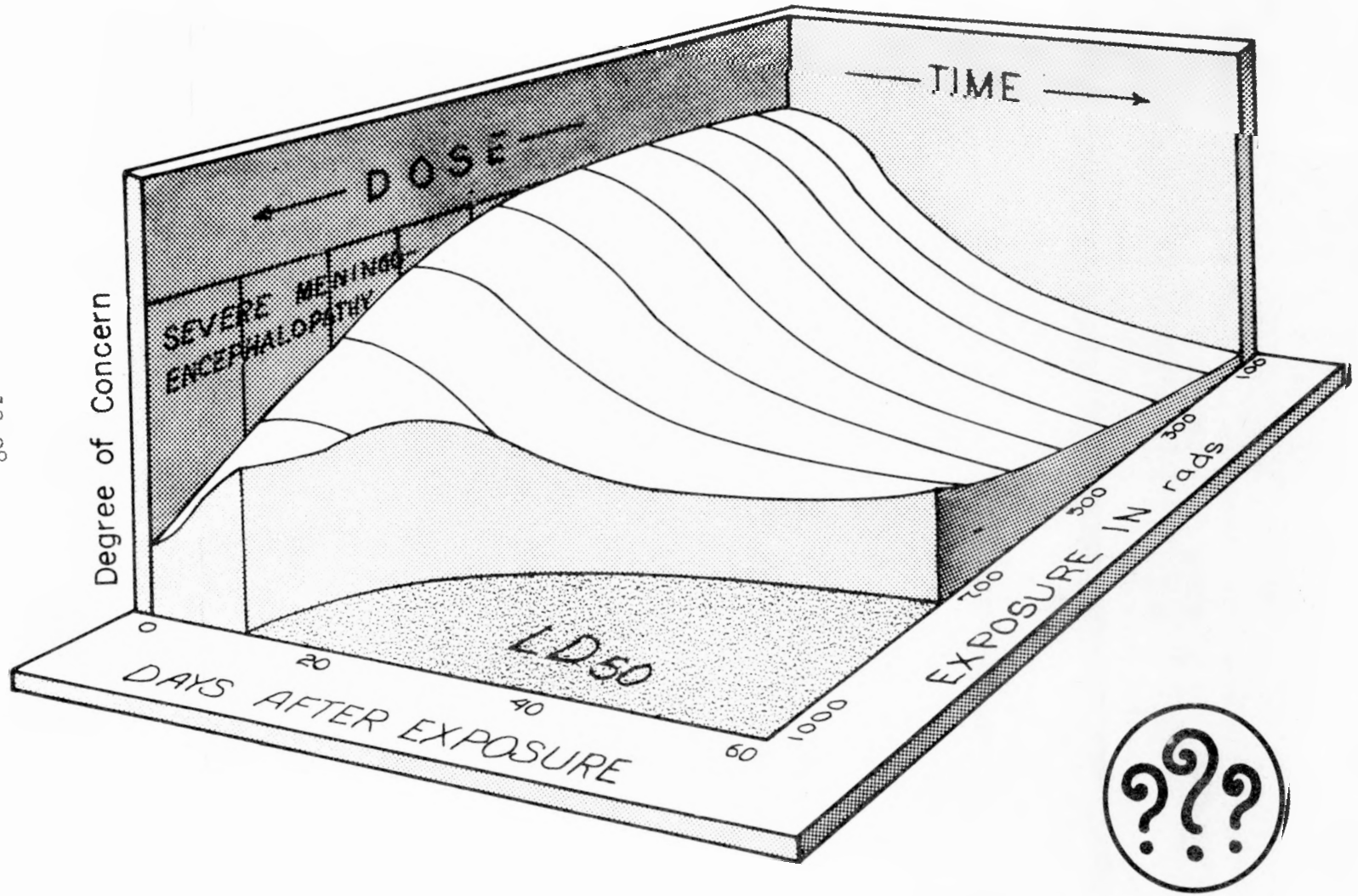
It is impossible to accurately characterize this fatigue, but it appears to occur in waves that run diagonally on the dose-time matrix. In very high-dose patients fatigue may be severe: a complete debilitation or coma. This severe fatigue is not properly the same as that described for shock. It is better described as a mild meningo-encephalopathy, since it is more like the kind of debilitation described in mild infections of the meninges. At lower doses patients describe the fatigue as a "washed out" feeling; they tend to stress the "weakness" in the thighs.

Although it is hard to characterize, fatigue is undoubtedly one of the important clinical signs to the physician. It must be correlated with and differentiated from the psychological effects of radiation. It is easy to say that it must be done, but it will almost be impossible for a physician to do this. The fatigue picture should be correlated with dehydration of vomiting. It might be related to the same pathologic physiology that causes the decrease in white cell counts.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

8



PSYCHOLOGICAL UPSET

ORINS - MB - 59

8. Psychological Effects

The psychological effects of accidents (and radiation?) are important but intangible. The reactions of patients to industrial accidents usually begin with fear of death. If anything, the high-dose patients might be least bothered since they are either comatose or hyperactive but there is an initial fear that results from the accident itself. Shortly after this fear has subsided there will be a psychological upset that is definitely related to the publicity on the accident. Much of this publicity will refer to predictions of dire events in the future. Along with any publicity there will be rumors. Patients hear and have a tendency to believe every rumor that occurs. One of the most useful items in therapy that the physician can give to the patient is reassurance on the falsity of rumors.

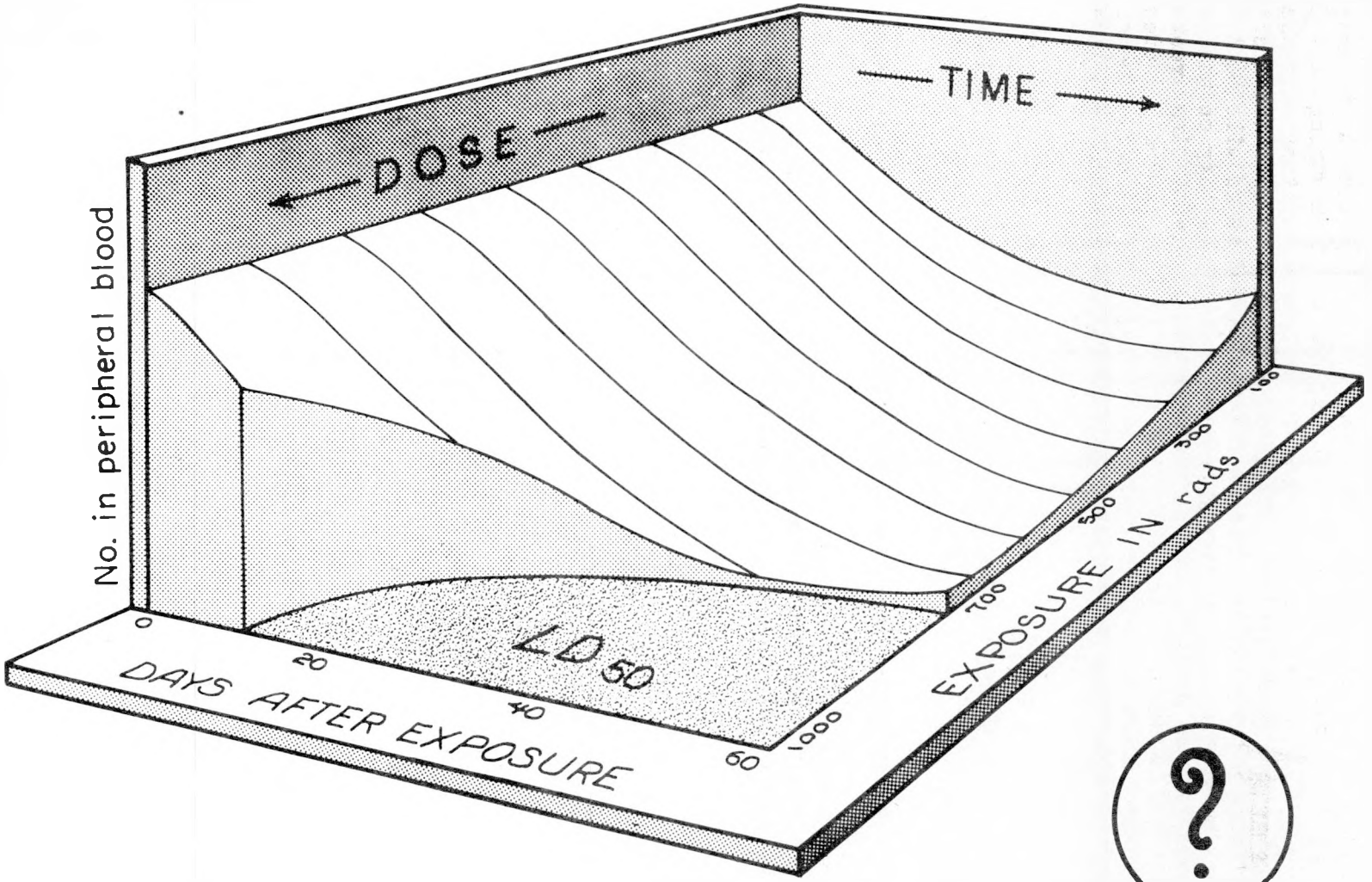
In accidents involving many people an additional set of psychological factors become important in relation to the death of other patients. Epilation also may cause additional psychological upsets unless patients are prepared for its appearance.

One of the worst features about a radiation accident at the present time is the fact that many people are going to be upset. It is essential in the proper care of patients that nobody but the physician and close friends be allowed to "see" the patients. The tendency for every administrative official and every government and state investigator to have to "see" the patients is dangerous. Probably the most important feature in treating psychological upsets is to see to it that the hospital is not turned into a zoo.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

9



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PLATELETS

9. Platelets

The platelet count is the one diagnostic procedure that the clinical pathology laboratory must do frequently. The standard techniques for estimating the number of platelets are not sufficient. It is necessary to count platelets, but the usual method can be misinterpreted. As long as there are sufficient platelets on a slide, the statistics of counting are good enough for diagnostic purposes by ordinary methods. Nevertheless, when one begins to count three or four platelets and multiply this number by a large factor, the statistics of counting are sufficiently variable to cause confusion. The interpretations of "no" platelets or "many" platelets over short spans of time are not really interpretations of physiological changes but are interpretations of statistics. When platelets are at a very low level, either the physician must interpret routine counts with an appreciation of inevitable statistical variation or a more complex and more exacting technique of counting should be used.

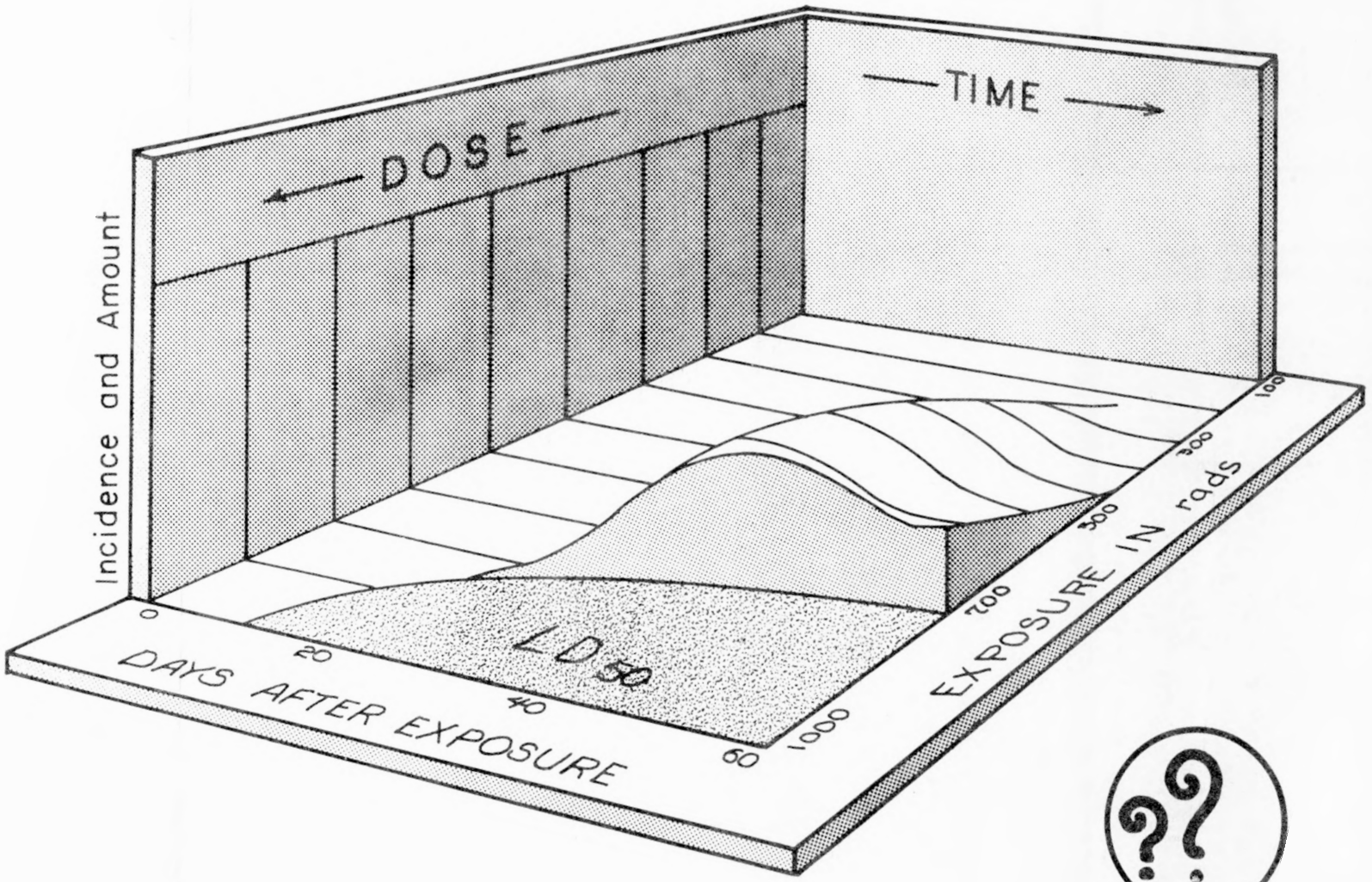
There is some question about the existance of an initial mild increase in the number of platelets. Still, since this increase is not important diagnostically, or prognostically, it is probably an academic question. The essential feature about the platelet count is that there is a continuing decrease that might start as late as a week or two after the accident.

The platelet count is not an absolute indication of the onset of bleeding. It is, however, a good indication that this is the time at which the bleeding might begin. Therefore, the platelet count extrapolated into the future is an indication of when blood transfusions may be necessary. Usually the platelet count will not show a real recovery for many months after the accident. Even so, an early indication of recovery (if it is not a statistical aberration in counting) is a good indication that the dose of radiation was not high. The absence of bleeding is not so good an indicator. Once there has been a real beginning of recovery of platelets, the acute phase is probably over with and there is little danger of future bleeding. The platelet count, therefore, is the best diagnostic sign in the late care of the acute radiation syndrome. Since there seems to be no other deficiency in the clotting mechanism, the administration of platelet-enriched-material is the indicated therapy if bleeding is likely.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

10



BLEEDING

10. Bleeding

Bleeding is a hazard of a few days in the fourth or fifth weeks after a radiation accident. It is almost invariably correlated with the disappearance of platelets from the circulating blood. It usually does not occur at less than a few hundred rads. It may not occur at medium doses unless something triggers the bleeding mechanism. In the few patients studied there does not seem to be any obvious fault in the clotting mechanism (other than the low platelets). It appears that the reasons for the patients' not bleeding are less well understood than the assumption of good reasons for their bleeding.

The common story is in patients who have received a significant dose of radiation. There are small patches of petechiae, "pink tooth-brush," easy bruising, but a real gross hemorrhage does not appear to be a prominent observation in the sublethal range. With high doses there may be gastrointestinal bleeding that is of much greater significance. Nevertheless, since bleeding is one of the things the physician can treat, it has assumed what is probably a more important place in therapy than is truly necessary. Bleeding is a development that we were afraid of, and prepared for, in the Los Alamos, Marshall Islands, and Oak Ridge accidents. However, it does not appear on hindsight to have been a very important part of the clinical picture. Needless to say most hematologists do not agree with my de-emphasis of the importance of blood in the low-dose range.

THE ACUTE RADIATION SYNDROME IN MAN

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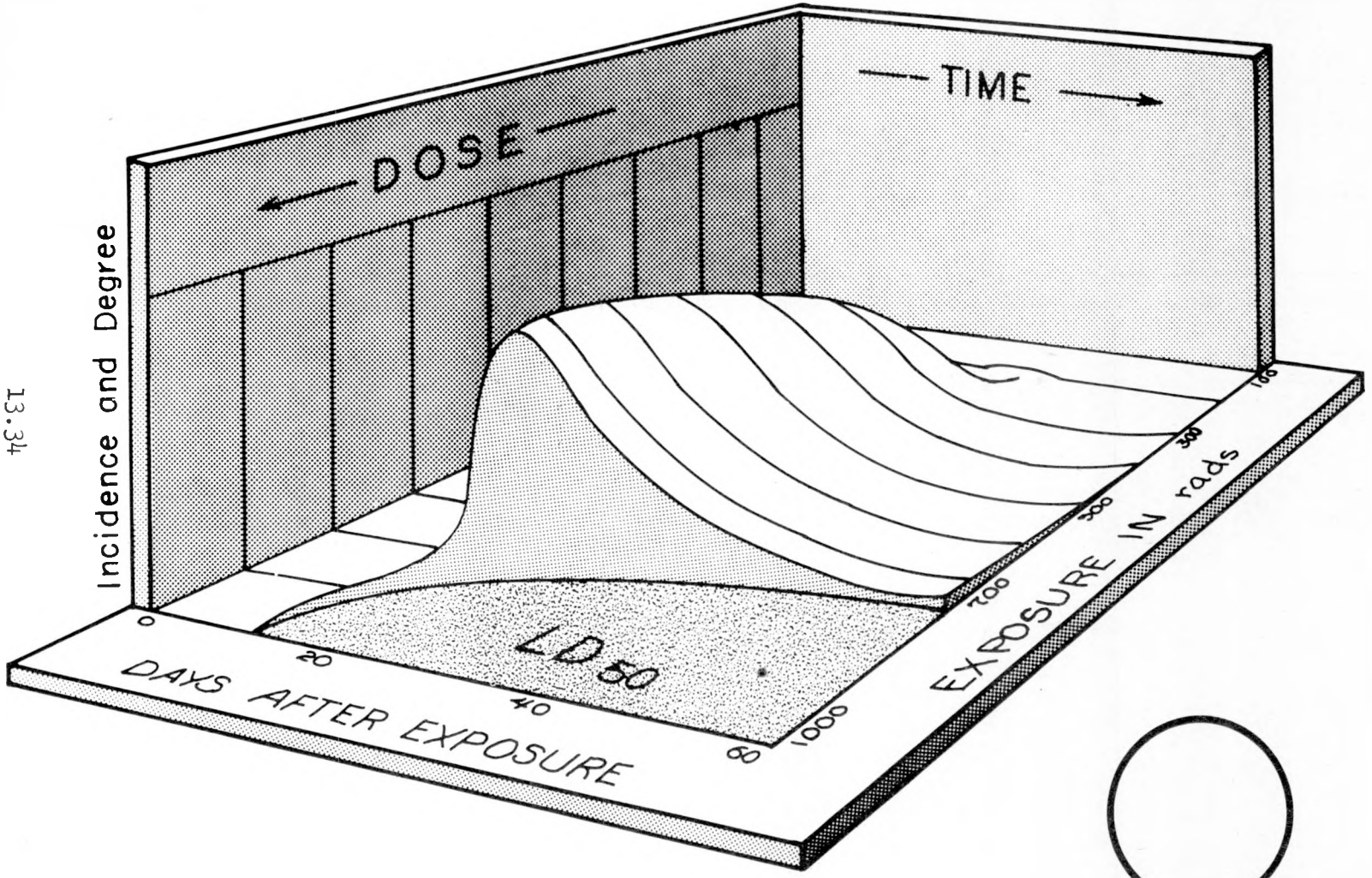


EPILATION

11. Epilation

With significant doses of radiation, epilation will suddenly occur on the seventeenth to twenty-first day. It seems to occur later with lower doses and is more severe with higher doses. Epilation is not an important clinical sign, and has little prognostic significance. There is always a regrowth of hair within a few months. (But radiation does not cure baldness.)

It appears that epilation does not occur at less than about 200 rads. It becomes progressively more severe with higher doses of radiation but not linearly. There is considerable individual variation. There is also considerable variation in susceptibility to epilation over various parts of the body. The occipital region of the scalp seems to be most commonly affected. In many patients tenderness of the scalp precedes epilation; patients describe a mild pain on stretching the scalp. In some patients the hair loss is generalized. This is a loss of hair from the legs and arms first noticed as shedding on the bed sheet.

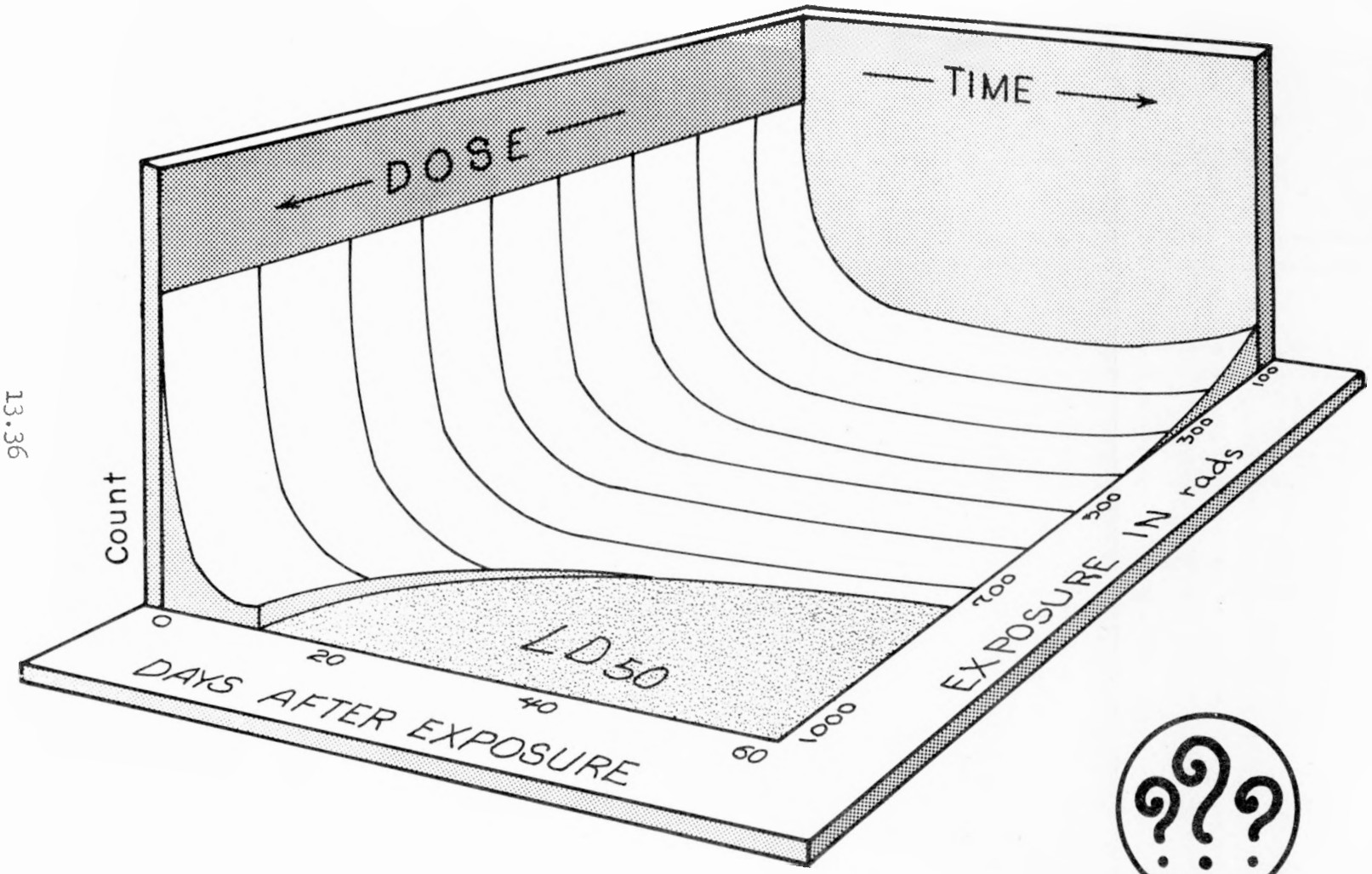
Attempts have been made to explain the distribution of epilation on the basis of dosimetry. These attempts, however, have been fairly unsuccessful because of the correlation of epilation to depth dose, which in turn is correlated with energy; and superimposed on these correlations various parts of the body seem to be more susceptible than other parts. The epilation spoken of in the radiotherapy literature is usually due to a large dose and is complete within the confines of a beam. Many radiation accidents will be at much higher energies and will not be confined to specific areas of the body.

The real importance of epilation lies in its visibility. It will be noticed by the patient and his friends; it will be suspected and looked for by the newspapers; and it will be the subject of ominous rumors. Apparently it is a sign that a significant dose of radiation has been received. Still, when epilation occurs late and is patchy and incomplete, it is usually a good prognostic sign that the dose was sublethal. The most important point that the physician must remember about epilation is that the patient must be reassured that it is temporary and might be a sign of impending recovery. This is probably not true when the epilation occurs very early and is complete.

12 CLINICAL FACTORS

THE ACUTE RADIATION SYNDROME IN MAN

12



SPERM COUNT

13.36

12. Sperm Count

The sperm count is an item that the physician probably will never have sufficient information on but will be a headache to explain to the patient and his wife. It is probably necessary to explain carefully that there is a distinct difference between impotency and sterility. Radiation, except in lethal doses, does not seem to affect potency. In the sublethal range (probably even at very low doses) it does induce sterility. Little is known about human sperm counts after irradiation. Extrapolation from animal work and a few human measurements indicates an apparently rapid decrease in the sperm count and a slow recovery. The decrease is probably almost immediate. Recovery in man probably takes many months. It appears that sperm counts in patients with doses of less than 100 rads return to normal faster than in patients with much higher doses. This is not certain, however. There is no correlation of sterility with fatigue; however, there might be a correlation of potency with the fatigue and psychological factors.

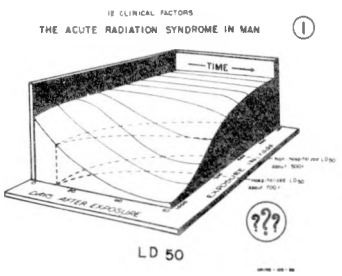
Associated in discussions with the patient concerning his sterility will be questions concerning future genetic effects. There has been an overwhelming publicity drive on the deleterious effect of radiation on sperm cells. All of this is probably true as it is stated by the geneticists. On the other hand, the impression one gets is not necessarily true. About 30 to 80 rads to the genetic cells in some animals will double the mutation rate. This sounds ominous until you realize that the mutation rate is normally about 10 in a million normal conceptions. Most of the mutations caused by radiation, in addition to these 10 in a million chances, will probably be automatically lethal. Therefore, the increase in mutation rate is a matter of increasing the chances of a malformed baby from 10 to 20, 30, 40, or even 100 in a million. This is still an exceedingly small chance and the best advice that can be given the patient is for him to forget genetic effects unless he is academically interested in the science of genetics.

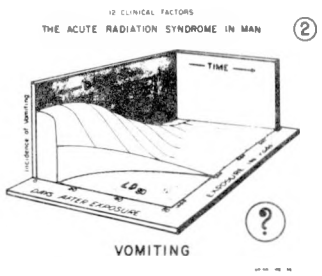
Related to genetic effects is the question of leukemia and cancer. These two subjects are on even more shaky foundations than is the mutagenic effect of radiation. It should be explained to the patient that we are not concerned with what happens in mice, spiderwort, or fruit flies but are concerned only with what happens in humans. An enormous number of patients have been treated with very large doses of total-body irradiation (as in cancer of the cervix) with no appreciable increase in the incidence of leukemia or of cancer. Apparently the production of leukemia and cancer in the human demands very long exposures, very high doses, or a very special genetic constitution. When the question of leukemia in radiologists is raised, the best answer is probably that radiologists are exposed over many years. The second answer is that statistics might not be true when the age specific death rates are mentioned and that all the talk concerning leukemia in radiologists is based upon very few cases of leukemia. When the question of the radium dial workers is brought up, the answer is probably best made

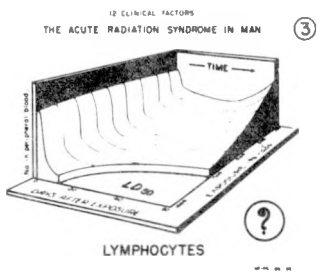
by pointing out the chronicity of radium toxicity. When the strontium poisoning story is brought up the answer is probably best made by pointing to the congressional hearings where the consensus seemed to have been that strontium poisoning is a fear, not a fact.

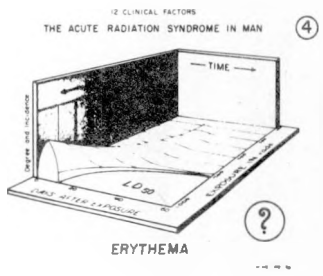
The discussions concerning the sperm count should not be downgraded in importance. They are intimately related to the psychological fears of radiation and these questions will probably cause the physician more trouble than any of the real pathological effects of radiation.

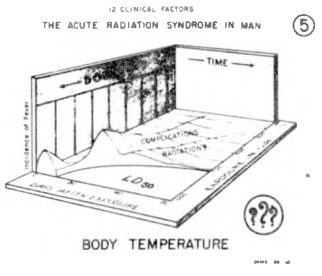
THERAPY
IN
THE CLINICAL ACUTE RADIATION SYNDROME IN MAN

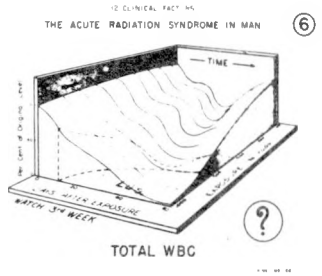


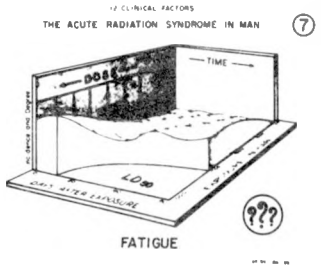


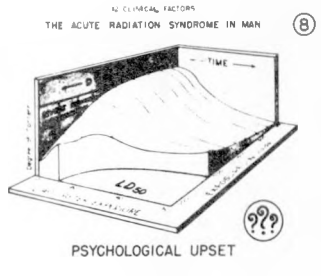


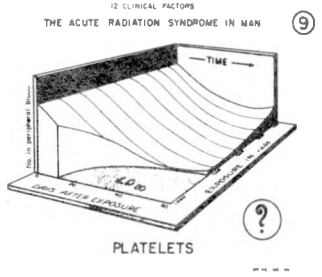


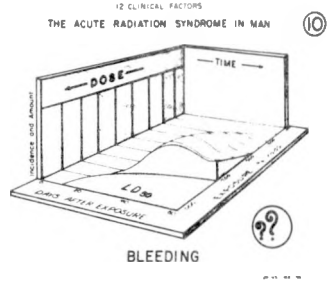


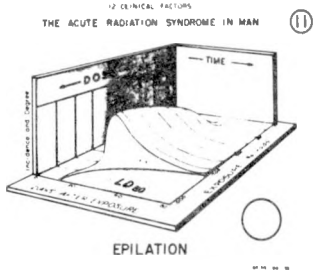


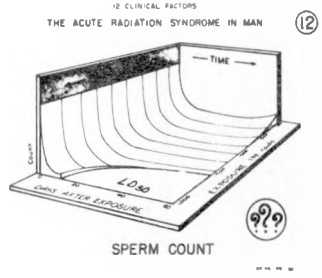












RECOMMENDED THERAPY
???

FIRST FEW HOURS

Hospitalize at 100r
Sedation
Anti-emetics if indicated

FIRST FEW DAYS

Bed rest
Sedation
Anti-emetics if indicated
Electrolytes if indicated
Ataraxis if indicated

? Consider bone marrow ?

FIRST FEW WEEKS

Rest
Sedation

Be prepared to give fresh whole blood
Be prepared for antibiotics
Be prepared to give bone marrow

HUMANS AND MICE ARE DIFFERENT ANIMALS

Summary of First Twelve Graphs: Recommended Therapy. There is no specific therapy for acute, severe radiation damage since there is no specific major pathology. All the treatment is symptomatic. A most difficult kind of therapy is necessary, and this is prohibiting yourself from doing anything that might be damaging to the patient. In the range of less than a few hundred roentgens of exposure (we'll say 250 r), probably no therapy is desirable other than reassurance to the patient and mild sedation. In the range of more than a thousand roentgens, probably nothing can be done effectively. It is possible that some of each type of cell in the body has been more or less damaged. The only logical procedure is to make the patient comfortable, to treat vigorously every symptom that appears, and to use any and every experimental procedure that appears to be indicated. In most patients with very high doses of radiation, the symptoms will develop rapidly and any therapeutic procedure will probably be done too late unless anticipated.

It is in the dose range of 250 to 1000 rads that medical therapy can be of real value. In the light of the large amount of work being done on experimental therapy, there will be demands for the physician to attempt procedures that might be more dangerous than the radiation itself. Most patients who absorb less than 500 rads are not in a real life and death danger from the radiation itself. Their danger is from the complications of the radiation accident. These complications usually are treatable; however, in the higher dose ranges it will sometimes be necessary to apply therapeutic procedures on the slightest clinical evidence, and before there is a real clinical indication. The physician should tend to be somewhat more conservative when the dose is less than 500 rads. When the dose is more than 500 rads, the entire picture is more rapid, more severe, and the therapy should tend to be somewhat more radical.

During the first few hours we recommended without question that the patient be admitted to a hospital at an exposure of 250 r. But physicians should realize that the establishment of a 250 r exposure can seldom be more than a poor estimate during the first few hours. The physician can do little to help the health physicist in making this estimate. Vomiting, if it does occur very early, is probably an indication of a very high dose. There may be no drop in the lymphocytes until after hours have passed. If erythema is present, it is probably indicative of an extremely high dose.

If the radiation is accompanied by a neutron exposure, a sodium activation will give an immediate hint of the level of exposure. It is recommended that calibrated total-body counting systems be available for immediate use. This is the one instrument that can give an immediate partial answer, but only in neutron exposure. Hand-monitoring devices can easily be misinterpreted, and should be used with caution. Still, since the situation in any accident will be so confused during the first few hours, it is probably better to admit all patients to the hospital until a reasonably accurate estimate of dosage is achieved, and than to

keep the patients with more than 250 rads in the hospital.

Sedation is indicated even in the very low doses.* This sedation may be mild and conservative at very low doses and become more vigorous as the dose estimate increases, or as the appearance of the patient indicates.

In low exposures there might be some purely psychological vomiting. It is probably better treated with sedation than with antiemetics. If, however, the vomiting is severe and apparently will be prolonged, and especially if the estimates indicate very high doses, it is probably valuable to give antiemetics even as a prophylactic procedure. Probably the most important therapeutic procedure that can be performed during the first few hours is to resist the temptation to load the patient with blood, drugs, and synthetic metabolic poisons.

During the first few days, after the initial period of confusion has passed, it should be possible to distinguish the very high-dose patients from the very low-dose patients. The indicated therapy at this time is bed rest and sedation. During this period there should be enough indication from the pattern of vomiting that antiemetics are either indicated or not. It should be apparent from the fluid balance of the patient that electrolytes should or should not be given.

It might not be apparent from the temperature charts that the patient has an impending infection. Antibiotics are probably not indicated in very early fever, and even with an early estimate of low dosage, the physician probably should not give antibiotics during the first few days. With an estimate of very high dose, the use of antibiotics is probably merely an added burden to the metabolism of the patient. I don't know how the decision can be made in the important medium-dose range. It is during this period that the treatment of the psychological upset of the patient is most necessary. In addition to sedation, ataraxis is probably indicated if the patient is unusually upset.

During the first few days the question of bone-marrow replacement should be considered. It was thought that bone-marrow replacement could be done only within a few days after total-body irradiation, but the Yugoslavian patients treated in Paris gave the first proof that this could be done in man. The French physicians gave bone marrow one month after the accident. The immediate results of this experience indicated its value, but the long-term results are unknown. Bone-marrow replacement is not a simple procedure, and it is not without some danger. Since most patients in the medium-dose range are already in great danger, it will be difficult to compare relative risks. It is not certain that

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* V. P. Bond points out that he has killed irradiated dogs with only a small fraction of the amount of barbiturate that would be only anesthetic for a normal animal.

bone-marrow replacement is valuable in humans. Neither is it certain that it is not valuable. Probably the only way in which to make the decision is to make a guess about whether the irradiated bone marrow is being depressed with rapidity that indicates very high dosage. If this is backed up by the health physicist's estimate, then we would be inclined to say that bone-marrow replacement probably should be attempted if the dose is more than 600 rads. If the dose is less than 400 rads, it probably should not be given. If the dose estimate is between 400 and 600 rads, the judgment should be based upon the rapidity with which the bone marrow is being depressed, and upon the severity of the vomiting.

Toward the end of these first few days, many patients in the medium-dose group will appear to get better. There will be a temptation to let them out of the hospital, especially in the low-medium dose range. However, experience has shown that all these patients will experience waves of fatigue and that this is a very real symptom indicative of pathologic changes too obscure for us to understand at the present time. In anticipation of this fatigue and the very serious consequences of physical labor during this period, the important thing in therapy is rest.

During the first few weeks after an exposure, there may be many more hints at the dose the patient has received and the pattern that he is following. The total neutrophil count will probably be declining steadily and the platelet count will indicate the onset of hemorrhagic complications. Rest and sedation are still indicated. The platelet count will indicate the necessity for preparing for blood transfusion. The temperature charts might indicate the necessity for using antibiotics. There is a sufficient amount of animal experimentation and human experience to indicate that fresh whole blood is decidedly superior to bank blood. Bank blood is far superior to blood substitutes. In an emergency anything might be valuable.

One purpose of blood transfusions is to replace blood lost during actual bleeding. It should be remembered, in giving fresh whole blood, that in part this is replacing destroyed platelets, but that platelets are only a part of the clotting mechanism. In part, you are also replacing red cells that have been lost in the circulation. Since some of the bleeding tendency is due to increased capillary permeability, the overloading of the patient with blood might be just as damaging as not giving any blood. Fresh whole blood should be given conservatively. Platelet preparations are probably not so good as fresh whole blood since they correct only one phase of the pathology of bleeding. This is a subject under as intensive investigation as in bone-marrow transfusion. It is likely that the prophylactic use of "platelet-enriched plasma" will be a subject for detailed concern to the physician during the third week.

There seems to be a tendency for the development of relatively minor infections. Since the total neutrophil count is decreasing early

during the first few weeks, infections should be treated with conservative doses of antibiotics. There have been indications that patients who have received radiation are more susceptible to drug reactions than would normally be expected. It should also be remembered that there is some evidence that patients can be sensitized to foreign platelets. The patient's own blood is always better than any foreign blood, but only if he has enough to maintain himself. A conservative rule to follow during the first few weeks is that there should be a plain and unmistakable indication for anything that is injected into the body.

Four Contamination Modifications

Up to now we have been speaking of relatively short bursts of pure gamma and neutron exposures. It should usually be expected that, in addition, at least a mild contamination will accompany the radiation exposure. Where contamination accompanies irradiation some of the clinical signs and symptoms are modified.

Most contaminating isotopes will settle on the sticky surfaces of the body, in folds and crevices. It is very easy for this contamination, especially if it is applied with explosive force, to penetrate clothing. The Marshall Islands experience cannot be taken as typical because the fallout contamination settled to the earth slowly. The Oak Ridge accident experience cannot be taken as typical because the contamination was almost infinitesimal. If the contamination is due to vaporization it might be an internal problem. The early Los Alamos accidents cannot be taken as typical because there was no reason for believing that there was a contamination. The Chalk River reactor accident, even though it did not involve contamination of humans, can be taken as a type of accident that might be typical. In this accident most of the contamination was in liquid form. Here, it not only would have penetrated clothing, but would also have settled in folds and creases of the body. Most of this kind of external contamination can be washed off easily. In considering contamination with radioisotopes, it is necessary to specify the energy of emission, the kind of radiation, and the half life of the material. Phosphorus-32 contamination will give an entirely different picture from cesium-137 contamination for purely physical reasons. Carbon-14 is entirely different from sulphur-35 contamination primarily for metabolic reasons. A definitive statement on the contamination dosimetry is a very complex problem. Nevertheless, when it is superimposed on a total-body irradiation picture, we can make a few generalized statements.

Vomiting and Nausea. It appears that when there is significant contamination along with total-body irradiation, the vomiting and nausea picture is about the same as that of total-body irradiation except that it appears at what may be called lower dosage. This is probably not a true lower dosage, but appears so when the estimates of dosimetry are based on total-body gamma irradiation. It appears that diarrhea is not

an important part of the total-body irradiation syndrome between doses of 100 and 1000 rads, but that it is a part of an internal contamination syndrome at what might be called doses lower than 100 rads. The diarrhea that occurs with external exposures appears to be a feature of only overwhelming high-dose levels. When there is bleeding into the gut, the bleeding itself may cause a kind of diarrhea.

Total Neutrophil Count. The picture shown by the total neutrophil counts is much the same with or without contamination. Still, when contamination is significant, the irradiation from radioisotopes may last longer. The depth of depression in white cell count may occur at a later period. Also, but probably because of the confusion in calculating the dosage, the entire picture appears to be moved toward the lower-dose levels.

It will always be difficult to distinguish an internal-contamination irradiation from a neutron-induced irradiation, but this can be done with adequate spectrometry. The neutron-induced sodium irradiation is at a relatively high energy and its half life is only a little more than a half day. The biological half time of most of the gamma-emitting fission products is many days. Usually the component of total-body irradiation dosimetry from the induced sodium is negligible in comparison to the initial total-body irradiation caused by the neutrons themselves and their accompanying electromagnetic emission. By the time the patient gets to the hospital, the total-body irradiation from the induced sodium will probably be negligible except that it is a useful diagnostic aid during the first few days. This might not be true of contamination radiation accompanying a total-body exposure. Since it is so easy to determine external contamination by simple wipe tests in the folds and creases of the body, probably one of the first therapeutic procedures, if there is evidence of contamination, should be a thorough washing of the outside of the body with soft bristle brushes, mild detergent solutions, and flowing water.

Skin and Hair. In general, depending on the degree of contamination and rapidity with which it is washed off, the skin and hair signs and symptoms are the most obvious features of a contamination exposure. Apparently when the contaminating radioisotopes are not removed from the body, there will be a mild itching soon after the exposure. This, however, should probably never occur in an industrial accident where a hospital is available. If the material is not washed off quickly, erythema might develop sooner, with greater frequency, and to a greater degree. It will also appear at what are called lower dosages. Again this is probably a confusion in the semantics of talking about dose rather than a true low-dose event. Epilation will occur more frequently with contamination and may be more complete than in external irradiation.

Where there is actual skin damage, the possibility for infection is greater. This should be treated by the usual external methods and, if indicated, with antibiotics. One of the features of visible skin

damage will be the later cosmetic effects of this damage. The skin will probably be somewhat discolored; subcutaneous fibrosis is expected only at very high doses, but it should be remembered that the local dose in skin damage is probably much higher than the range of numbers we are talking about in total-body dosimetry.

Internal Contamination. One of the serious problems that accompanies a contamination exposure is the almost inevitable internal damage to lungs, gut, and kidneys. If there is any contamination in the air, there will be some absorption through the mucosa, some through the lungs, and much absorption into the gut. Direct absorption through the skin is always possible. In a substance like plutonium, an exceedingly small amount absorbed into the body can be dangerous. In a substance such as cesium 137, the danger is much less. In the nonabsorbable salts of strontium, the danger is probably related to the dose to the gut wall. A soluble and absorbable salt of strontium will have a far greater danger.

In general, indications of internal damage will occur much later and might be more prolonged than an external contamination. With internal ingestion, or even inhalation, the proper therapy seems to be early catharsis, and the promotion of diuresis. The use of various chelating agents is still in an experimental stage. Although they cause a tremendous increase in the number of counts that are excreted of various radioisotopes, they do not seem to change greatly the total-body irradiation picture. Still, these are the best agents that are now available and they probably have to be used since any reduction in the contributing dosage from internal emitters is probably of value. The same is true of blood-washing techniques.

Four Very Important Frustrations

Additional factors are involved in the care of patients exposed to radiation accidents. These factors might not at first be considered important by physicians, and are not usually discussed in medical textbooks. Still, they can take up time and are extremely important in the ultimate care of patients.

Publicity. The first of these factors is the problem of publicity. In radiation accidents and especially in and around atomic energy plants, publicity is a natural by-product. This can be explained partially. First of all, atomic energy was Sunday Supplement Science for a period of about 50 years. "An ocean liner can be driven across the ocean by the energy contained in a cup of water." This statement has been repeated so often that it is almost a cliche in the public mind. "There are tremendous forces in nature." Nobody knows exactly what this means except a few theoretical physicists and the statement is completely out of the realm of practical reason, yet it is a nice catch phrase that has conditioned the public to be aware of tremendous power and with it a tremendous danger.

Second, the "force of the atom" was impressed upon the public mind by a number of atomic bombs. The energy released was correlated indelibly with death. Sunday Supplement Science was put on the first page.

A third item is that useful atomic energy (radioisotopes and power production) was combined for many years with an unnecessary bureaucratic and very necessary military secrecy to mix the idea of radiation with the idea of explosive danger. All these factors combined have made atomic energy synonymous in the public mind with horrendous danger. These features, combined with the amount of money available for safety, has made a press field day for impending doom.

Shortly after any radiation accident there will be a demand for publicity. This publicity will usually be handed out by people other than the medical department, and it will invariably be released to the newspapers by persons other than those on the public relations staff in the form of "tips" by nonpaid correspondents of newspapers. Physicians might be called on to supply the "blood and gore" details. The only safe comment that a physician can make over the telephone is "no comment, see the public relations officer."

Shortly after the accident has occurred, the public relations office of any atomic energy installation will take over and this is where all the publicity should emanate from. Any newspaperman can "and it should be assumed that he will" make a fool out of any physician. Public relations officers have a special training and flair for handling newspaper people. Just as much training is necessary in this field of specialization as in taking care of patients.

After the initial description of the accident has appeared in newspapers, there will be an inordinate demand for names. This publicity connected with any poisoning case can be totally irresponsible. The story of the press relations in the Houston incident early in 1957 is a perfect example of the hole a physician can get into by releasing names. The dramatization of the Houston accident for commercial television shows how an otherwise not very dangerous accident can be blown up into monstrous proportions. I repeat, the only safe thing for any physician to say over the telephone is "no comment, see the public relations officer."

Much of the publicity will die with an evanescent half life. However, the occurrence of late deaths due to the accident is an automatic trigger for a revitalization of newspaper interest. Poor administrative policy long after the accident can lead to the republication of reports. There is definite necessity for administrative reports and physicians will have to participate in their preparation. Nevertheless, it is an administrative responsibility to see to it that these reports are not deleterious to the care of the patient.

In the Oak Ridge accident there was only one instance of a serious breach of the handling of publicity and this did not come through the Oak Ridge office. A national weekly news magazine published statements that were seen and read by all the patients, and were based upon the worst kind of ignorant speculation. As a result of this unfortunate publicity, the psychological problems of the patients were increased.

Publicity is unfortunately necessary. Many people connected with the atomic energy industry have a real interest (and it is desirable that they should have) in accidents. The objective of the physician should not be to give the least possible information. It should be to give the most information consistent with the welfare of the patient.

Administrative Upset. It is probably inevitable that there will be an initial shock to administrators. In any large atomic energy program, the safety program is a major concern. There are rules and regulations that must be followed. Some of these rules and regulations may appear stupid to physicians whose first concern is to take care of the patient. Most of the early administrative upset will appear to be meddling in medical care. It is due to an essential concern on the part of the administrators for the welfare of the patients. In a well-run organization it will disappear rapidly. Physicians will not be bothered with administrative details until death occurs because of the accident. Death must be handled administratively with as much attention to details as it must be handled medically. The administrative details are not his business, but are the physician's protection.

There will be a third wave of administrative concern long after the accident has happened. This wave will be primarily related to necessary reports, workmen's compensation, insurance, and legal details.

The only safe procedure for a physician during administrative upsets is to live through them and to be thankful that the administrators are concerned.

The Need for Health Physics Help. There is a great need for help in dosimetry from the health physicist immediately after the accident has occurred. This immediate help is most necessary in the medium-dose range of around 500 rads. In this range treatment probably has the most effect. In the very low- and very high-dose range, it probably doesn't matter much whether or not the health physicist gives a correct estimate of the dose.

It is a general impression that health physicists have a tendency to give low estimates immediately after an accident and high estimates shortly thereafter. These estimates are invariably based on theoretical reconstructions, or on estimates of what should be in the area, or on early film badge readings. They should be accepted as estimates only. The physicians should realize that a health physicist usually cannot make good estimates in less than 24 hours. After he has had time to

gather evidence and reconstruct the entire incident, the health physicist should be closer to the truth. The best way for the physician to second guess the health physicist's early estimate is by the degree and severity of vomiting.

By the time the health physicist can physically (often this must be theoretically) reconstruct the accident, many of the decisions that must be made during the first few hours have already been made and the health physicist's usefulness decreases for the time being. After the first few hours the clinical course of the patient will be a better estimate of dose than any reconstruction by physicists.

One possible modification of this statement is in installations where a total-body counter is accurately calibrated for neutron activations, or for specific contaminating isotopes. Such a machine should exist in any hospital that may be called upon to take care of radiation accidents. Urine, blood, and wipe-test analyses, if done immediately with calibrated instrumentation, can be finished in time to give reasonable estimates of the type and amount of contaminating activity. Still, where there is no contamination and no neutron activation, such studies usually are of little value.

In most atomic energy installations a system should be set up to do blood, urine, external secretion, and total-body counts rapidly. Such physical tests, in the near future, will be valuable in estimating both type of radiation and magnitude of dose.

It is difficult to give recommendations on the proper relation of the physician to the health physicist in the large-dose problem since there will be an unusual training expense for an unusual event. During emergency clean-ups, the health physicist is just as necessary to the surgeon as his anesthesiologist. He is a necessary partner to the internist during the critical hours when dosage is in doubt.

Another time at which the health physicist becomes a necessary part of the medical program is during the period immediately after the "possibility of bleeding." After this time signs of regeneration are usually unmistakable and the patients will probably be released from the hospital. At this time, medical reports must be made and these medical reports have to be correlated with the dosimetry and description of the accident. Since it is probable that few accidents will occur in the atomic energy industry, each accident becomes an item for careful study.

A final point of importance for health physics correlation is in the correlation of late affects. Although this is not a part of the acute picture, the paucity of information makes it essential that every radiation accident become a "study" in addition to a "therapy."

Therapeutic Frustration. There is no specific treatment for radiation damage. Neither is there any specific pathology. There are,

however, hundreds of research projects describing different kinds of exposures, in different species, in different dose relationships, over different time periods. Each of these will offer a different kind of advice. Much of this advice is good, but is not applicable to the human problem. This leads to therapeutic frustration.

Once it has been definitely established that the patient has received less than 250 rads, there is probably no need for therapeutic frustration. There is nothing the physician must do except to convince himself that the dose was less than 250 rads. When the dose is more than 1000 rads, there is probably very little that the physician can do.

The situation is similar to that of a surgeon attempting to treat a thoroughly crushed body. He attempts repair in the order of physiological importance of the symptoms and signs: for example, he treats bleeding before shock, shock before broken bones, broken bones before cosmetic defects. These are well known principles, but there is an extent of damage in which the surgeon does not expect to be successful. Neither should the physician expect to be successful with very severe radiation damage. However, there are still things that must be done. In the high ranges of radiation absorption, therapeutic frustration will come after the patient dies because on hindsight there will appear to be many things that might have been done, all of them based upon animal experiments that might have been applicable.

In the range between 250 and 1000 rads, therapeutic frustration is most prominent. In this range patients can be saved and therapeutic judgment might determine the difference between a good and a poor prognosis. The treatment is symptomatic but is based not only on the symptoms that have appeared, but also on those that are expected to appear. A treatment plan is suggested in the order of procedure that follows.

The first five steps in this procedure are obvious. Step number six contains the real essence of medical care. The physician must separate the various factors that enter into any radiation accident. He must decide whether the accident was with high- or low-energy radiation. He must decide this from what is, of necessity, inadequate information. He must decide whether the exposure was given over a short period of time or over a long period of time. He must also decide what kind of radiation and how much contamination should and can be removed.

No matter what therapeutic procedure is followed somebody will criticize it. This should be expected but should not be taken as a discouraging sign or lack of faith in therapeutic judgment. It is a good sign that many physicians are interested in the problem and that the therapeutic situation is in the midst of revision. One of the first things that a physician will learn when he takes care of a radiation accident case is that every other physician working for an Atomic Energy Commission contractor is immediately available for consultation and help.

Suggested Order of Procedure for Physicians in a Radiation Accident

DISPENSARY PHYSICIANS

1. Remove patient from radiation area.
2. Give immediate first aid.
3. Call for health-physics help.
4. Isolate patient to prevent contamination of others.
5. See that the danger area is closed off. This is not your business but you should be sure that it is done.
6. Sit down - throw out visitors - think - and answer two questions:
   a. Is the patient contaminated? With what? Neutrons?
   b. What is the level of radiation exposure?

	Contaminated:	Not Contaminated:
7.	Clean up contamination reasonably well.	7.
8.	Measure contamination in whole-body counter.	8.
9.	Put patient to bed.	9. Put patient to bed.
10.	Save all samples: clothes, blood, urine, feces, vomitus	10. Save all samples: clothes, blood, urine, feces, vomitus
*11.	Do routine blood counts.	11. Do routine blood counts.
12.	Keep patient in bed.	12. Keep patient in bed.
13.	Send patient to hospital if you suspect more than 250 r exposure.	13. Send patient to hospital if you suspect more than 250 r exposure.
14.	Brief the administrators and the public relations office.	14. Brief the administrators and the public relations office.

HOSPITAL PHYSICIANS

**15.	Save all samples.	15. Save all samples
16.	Do brief history and physical.	16. Do brief history and physical.
17.	Do definitive surgical decontamination.	17.
18.	Do emergency surgery. Health-physics help is needed and you may have to do 17 and 18 simultaneously.	18. Do emergency surgery if indicated.

(continued on next page)

19. Put patient in total-body counter.
20. Forestall iatrogenic exsanguination.
21. Start daily blood counts.
22. Give sedation if indicated.
23. Give antiemetics if indicated.
24. Do definitive history and physical.
25. Start bone marrow examinations (two times a week).
26. Call a meeting of physicians and health physicists.
27. Brief the administrators and public relations office. From this point on formal daily reports are desirable.
28. Call for consultation.
29. Go back to routine hospital procedures.

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* If the health physicist can guarantee less than 250 r exposure, draw 50 cc of blood for health physics. If he cannot guarantee less than 250 r exposure, do not draw any blood except for blood counts.

** Send 250 cc of urine (or as much as is possible from the first sample) immediately to the dispensary physician for health-physics analysis.