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CHAPTER IV

VOLUME 2C - PART I

CLINICAL LABORATORY EXAMINATIONS OF PLUTONIUM PROJECT PERSONNEL

by

Leon O. Jacobson, M. D. and E. K. Marks

[redacted]

Report Received: December 6, 1946
Figures Received: December 6, 1946
Issued: February 11, 1947

[redacted]

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I. Introduction

II. General Rationale of Clinical Laboratory Examinations and Other Health Procedures

III. The "Control" and "Work Hazard" Grouping of Project Personnel

IV. General Procedure Followed in Dealing with Clinical Laboratory Abnormalities

A. Leucocytes

1. Total leucocytes below 5,000 per cu mm
2. Total leucocytes above 10,000 per cu mm
3. Lymphocytosis
4. Neutrophils
5. Neutrophil - lymphocyte ratio
6. Monocytes
7. Eosinophils
8. Basophils
9. Immature forms

B. Reticulocytes, Erythrocytes, and Hemoglobin Determinations

1. Reticulocytes
2. Erythrocytes and hemoglobin in grams per 100 ml

C. Platelets

D. Sedimentation Rate

E. Urine Examinations

V. The Liaison Committee

VI. Clinical Laboratory Abnormalities Encountered

VII. Studies Made on Individuals with Leucopenia

A. Effect of Exercise on the Number of Leucocytes of the Peripheral Blood

B. Variation of Total Leucocyte Values During One Day

C. Effect of Adrenalin Injections on the Leucocyte Values of the Peripheral Blood

D. Sternal Bone Marrow Aspiration

E. Morphological Studies

F. Daily Leucocyte Counts Conducted for More Than One Year

VIII. Evaluation of Clinical Laboratory Studies Conducted on the Plutonium Project

A. Urine Studies

B. Hematological Studies of the Peripheral Blood

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[redacted]

[redacted]

IX. General Conclusions

A. Experiments on the Effect of Ionizing Radiation on Coagulation of Blood

B. Chronic Daily Exposure of Animals to Whole Body Gamma Ray in the "Tolerance Range"

C. Exposure of Humans to Single and Divided Doses of Externally Originating Radiation (X ray--whole body)

D. The Biological Effects of Long-lived Radioactive Fission Isotopes

X. Summary

[redacted]

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CLINICAL LABORATORY EXAMINATION OF PLUTONIUM PROJECT PERSONNEL

by

Leon O. Jacobson and L. K. Marks

I. Introduction

The inadequacy of the experimental and clinical data upon which the "tolerance dose" of various ionizing radiations has been based is pointed out in the Introduction and in Chapter IV of this volume. It was apparent to those of us who were charged with the responsibility of protecting the personnel working on the plutonium project from "overexposure" to ionizing radiation or the toxic effects of uranium, that no clinically applicable tests were known which could detect biological alteration in an animal or human exposed to doses of radiation or uranium isotopes in the "tolerance range."

The toxic effect of uranium which is discussed in detail in Chapter VI of this Volume and Volume 20, Part II had been emphasized by the work of several investigators(1)(2). The work of these investigators has stressed the toxic effects of uranium on the kidney when administered parenterally in minute quantities. No publications were available, however, on the amount one could expect would be absorbed from the skin, lungs, or gastrointestinal tract when such routes of entry were possible nor was information available on the expected biological effects of uranium compounds thus absorbed in small quantities from day to day. Calculations indicated that the radiation effect of uranium 238 even if it were absorbed would be relatively negligible unless deposition within the human body reached a total of approximately five grams. Thus, it was apparent that the toxicity of uranium was primarily chemical and clinical tests were needed to detect damage.

Certain facts were known regarding the biological effects of ionizing radiations. Beginning with the work of Heineke in 1903(3) the adverse effects of radiation upon the blood forming tissue and the reflection of such effects in the peripheral blood were recognized. Innumerable investigators have since studied other biological and

1194 50

clinical effects. The purely experimental data available, however, were confined largely to animal studies in which lethal or near lethal doses of externally applied X and gamma rays or fast neutrons were given either to a part or to the whole body as one (acute) dose or as closely spaced divided doses. The purely clinical data were likewise confined to reports of the effects of therapeutic doses of X and gamma rays or fast neutrons given to local areas of the human body and in relatively large single or divided doses. No deliberate studies in animals or humans had been reported in which chronic exposure to ionizing radiations was within the "threshold range." A few reports available from clinics and radium institutes indicated that, as far as whole body chronic exposure was concerned, the hematological constituents of the peripheral blood were the most sensitive indicators of radiation effect(4). These reports dealt exclusively with professional and non-professional staff concerned with the preparation of radium sources and the administration of radiations for therapeutic purposes. The amount of exposure such workers received over extended periods, however, was in most instances largely estimated rather than accurately measured.

The information available on the biological effects of radioactive isotopes deposited within the body was confined to experience gained largely from the radium dial industry and from the more recent therapeutic and tracer studies with the relatively short-lived isotopes such as P^{32} (5), $Sr.^{89}$ (6), I^{131} (7), and Na^{24} (8). Reports on the radium dial painters described patients with terminal anemia, radiation osteitis, and osteogenic sarcoma in whom the accumulated initial doses of radium were unknown and only the residual deposition was ascertainable(9a)(9b). The tracer and therapeutic studies with "short-lived" artificially produced radioactive isotopes were not directed toward the study of the more chronic general biological effects.

With this brief introduction it is apparent that to prevent overexposure of personnel to radiations and uranium toxicity, extensive prophylactic measures had to be undertaken and the degree of individual exposure and laboratory contamination constantly determined. The changes induced in the hematological constituents of the peripheral blood and in the urine were considered by most of us to be the most sensitive known indicators of radiation and uranium toxicity respectively. Consequently,

1945

the routine pre-employment examination and follow-up of all personnel working at the Metallurgical Laboratory at the University of Chicago in Chicago, Clinton Laboratories in Oak Ridge, Tennessee, and at the Hanford Engineering Works in the State of Washington, included studies of the peripheral blood and careful examination of the urine. However, an extensive program of clinical and biological investigation was instituted to find other interpretable and applicable clinical tests for incipient damage to the human body from these physically and chemically toxic agents. These latter investigations reported in detail in the Collected Papers of Volumes 21, 22, and 23 included such studies as:

1. Catalase activity of the urine of personnel exposed to uranium isotopes.
2. Urine and blood copro and proto-porphyrin determinations of personnel exposed to uranium.
3. Liver function tests of personnel exposed to uranium.
4. The effect of radiation on the phosphorus metabolism of the leucocytes.
5. The effect of radiation on the nail bed capillaries of personnel.
6. The effect of exposure to various radiations on the structure of the finger ridges.

II. General Rationale of Clinical Laboratory Examinations and Other Health Procedures

An extensive and continuous study of the peripheral blood and urine of the project personnel was undertaken. This was done in an attempt to discover evidence of incipient damage from chemically and physically toxic agents in personnel where unavoidable or accidental overexposure had occurred. We were aware of the fact that significant biological effects resulting from exposure to these agents and which could be detected by clinical observations invariably meant that serious damage to health had already occurred. As is emphasized in Chapters I, II, and III, prophylactic measures designed to prevent or minimize the danger of irreversible damage to the health of laboratory personnel from these agents were paramount. However, it was known that the degree of exposure to these agents could not be accurately anticipated in each individual case due to accidents, carelessness,

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and the like. Furthermore, we were to deal with certain materials such as plutonium the biological action of which was not known. We could only attempt, therefore, to emphasize measures designed to prevent or minimize damage to health from these agents and to carefully study the individuals concerned in order to discover any physical or laboratory evidence which could be interpreted as chemical or radiation toxicity. It must be pointed out that the results of the initial pre-employment study of each individual which included a history, physical examination, X ray examination of the chest, Wassermann and Kahn, sedimentation rate, routine examination of the urine, and peripheral blood were carefully scrutinized. Special attention was given to the advisability of employment of individuals who, for example, had evidence of renal tract abnormality on the basis of examination of the urine. Such individuals were rejected for employment or were employed and located in areas within the laboratory in which exposure to the uranium isotopes or radiations or both were negligible or absent. An attempt was then made to determine the nature of the abnormality. Individuals with hematological abnormalities found in the pre-employment examination were likewise specially considered. Individuals with a leucopenia but who were acceptable for employment in other respects were placed whenever possible in work areas wherein exposure to ionizing radiations was minimal or absent.

III. The "Control" and "Work Hazard" Grouping of Project Personnel

All employees once accepted for employment and placed in a particular job or position were classified in terms of their individual occupational hazard on the project in one of two groups namely, (1) the control group and (2) the work hazard group. This division was not made in terms of the usual understanding of occupational hazards but rather in terms of the hazards peculiar to the plutonium project.

The control group consisted of all employees working in areas in which exposure to radiations or chemically toxic materials was negligible or absent. This group included, for example, the administrative staff who worked in buildings or parts of buildings in which no work was done with physically or chemically toxic substances and who otherwise had no contact with such materials. Studies of the hematological constituents of the peripheral blood and urine were conducted on these individuals

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with regularity for purposes of comparison with the individuals working in areas in which these hazards existed. The number of individuals in the control group was actually comparable to that of the "work hazard" group described below. All individuals in the control group had blood and urine studies no less often than every six months. Hematological studies were made daily on certain control individuals for as long as two years.

The work hazard group consisted of all those individuals in the laboratory who were exposed or potentially exposed to the physically or chemically hazardous materials peculiar to the project. Since certain areas of operation on the project and certain types of work were actually or potentially more hazardous from the standpoint of radiation or uranium exposure, individuals were subdivided into essentially three groups: (1) those with only a potential or minimal exposure; (2) medium exposure or; (3) heavy exposure. This subdivision was arbitrary and on a relative basis. For example, a secretary who worked in an office adjoining a laboratory in which radioactive materials were studied was considered to be in a potentially or minimally hazardous area and laboratory examinations were conducted at monthly intervals while individuals working directly with the radioactive fission products day after day in amounts above the tracer level were considered in the "heavy exposure" group. The frequency with which clinical laboratory examinations were done in this latter group varied from daily studies to studies conducted every three months.

IV. General Procedure Followed in Dealing with Clinical Laboratory Abnormalities

To facilitate the operation of the clinical laboratories of the project, a guide was formulated which made it possible for the Chief Technician in each clinical laboratory to routinize the procedure of handling abnormalities which appeared in tests on personnel. This guide which is summarized below was instituted at Chicago when the project began operation and later at the Clinton Laboratories in Oak Ridge, Tennessee, and Hanford Engineering Works at Hanford, Washington.

A. Leucocytes

1. Total leucocytes below 5,000 per cu mm

Any individual whose total white count was found below 5,000 per cu mm

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whether in the "control group" or "work hazard group" had repeat counts at weekly intervals. If the situation warranted, particularly in the work hazard group, even more frequent counts were instituted, the individual work hazard was investigated and a decision was reached by the Liaison Committee. The functions of this important committee which made decisions relating to health matters is taken up in detail in paragraphs to follow.

With a return of the leucocyte values to the normal range in "control personnel" a repeat count was done again in one month. If still normal, a regular schedule of every six months was resumed. With a return to normal of the leucocyte value of individuals in the work hazard group the frequency of repeat counts depended upon the final disposition of the individual case (reduction in amount of exposure, removal from exposure, etc.).

2. Total leucocytes above 10,000 per cu mm

a. Individuals in the control group or individuals in work hazard groups whose total leucocyte count was found to be above 10,000 per cu mm had repeat counts at monthly intervals unless 2.b. was applicable.

b. In individuals in whom an acute exposure to irradiation had or was presumed to have occurred, a total leucocyte count and differential was made daily for one week and thereafter at weekly intervals as indicated by the results of the laboratory work done. Within the first 48 hours of such an actual or presumed exposure, even more frequent counts were taken as indicated.

3. Lymphocytosis

A minimum of 1500 lymphocytes and a maximum of 3400 per cu mm served as guides in repeating blood counts. A lymphocyte count of 1500 or less was checked daily as described in 2.b. if it was thought to have resulted from an acute exposure. If, however, such a value was found in the work hazard group and was presumed to be related to the chronic exposure, counts were repeated in one week. If still as low or lower, the frequency of repetition depended largely on the final medical disposition of the case (decision of

1145

the Liaison Committee). Lymphocyte values below the minimum in control personnel served as an indication for a repeat in a week and at monthly intervals thereafter until normal. If still normal in a month, the schedule of every six months was resumed. This schedule applied in general to total lymphocytes above 3400 per cu mm.

4. Neutrophils

A minimum of 2500 neutrophils and a maximum of 7400 per cu mm were considered to be the normal limits. Neutrophil values found to be 2500 or less were checked as per the schedule outlined in 1. If values were found to be above the maximum, repeated examinations were carried out as described in 2.a., unless thought to be due to an acute exposure in which event the procedure outlined in 2.b. was followed.

5. Neutrophil-lymphocyte ratio

In recording the leucocyte count and differential leucocyte count the per cent of each constituent as well as the calculated absolute number of the major constituents were filled in on the permanent report sheet (see attached form used by the Metallurgical Laboratory at the University of Chicago). The procedure for repeating blood counts when abnormalities in the absolute number of lymphocytes and neutrophils appeared was outlined above. The neutrophil-lymphocyte ratio varied considerably but for purposes of convenience and simplicity 1.2 was chosen as the normal value. Careful surveillance of this ratio in control and work hazard individuals was maintained. Trends in the neutrophil-lymphocyte ratio were often noted at a glance that were not obvious from observation of the record of the absolute numbers of these constituents.

6. Monocytes

Persistent or increasing monocytosis above six per cent, otherwise unexplained, was considered as an indication for a repeat leucocyte count and differential at monthly intervals.

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Name

Group

Section

Building No.

Age

URINE

Date																							
React																							
Sp. Gr.																							
Alb.																							
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Anisocytosis																							
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40																							
60																							
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7. Eosinophils

A persistent or increasing eosinophilia, otherwise unexplained, was considered as an indication for repeat determinations at monthly intervals. Individuals in whom eosinophilia (above 5 per cent) was encountered and thought to be related to the work hazard had leueocyte determinations and differentials at monthly intervals.

8. Basophils

No available information indicated that the number of basophils in the peripheral blood was significantly altered by radiation exposure. They were counted routinely, however, and if an abnormality appeared, it was considered specially.

9. Immature forms

Immature forms in excess of normal such as myelocytes, nucleated erythrocytes etc., appearing in the peripheral blood smear were considered as they arose and proper evaluation and disposition made.

B. Reticulocytes, erythrocytes, and hemoglobin determinations

1. Reticulocytes

Reticulocytes, in per cent of erythrocytes, were considered within normal limits if between 0.5 and 2.0. Estimations of reticulocytes were not made routinely but special work hazard groups and comparable control groups were designated arbitrarily and had reticulocyte estimations along with the other hematological routine.

2. Erythrocytes and hemoglobin in grams per 100 ml

Erythrocytes and hemoglobin determinations were made on the individual in the control as well as on those in the work hazard groups. The frequency of determinations in the latter group depended on the amount of exposure the individual was considered to be getting. The frequency of determinations in the control group is discussed below.

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The hemoglobin and erythrocyte values which were considered within

the normal range are:

	Erythrocytes (millions per cu mm)	Hemoglobin (grams per 100 ml photoelectric)
Male-adult	5.5 ± 1.0	16.0 ± 2.0
Female-adult	5.0 ± 1.0	14.0 ± 2.0

In the event that values according to these standards were found to be abnormal and the abnormality ascertained found to be unrelated to work hazards the individual was referred for investigation and treatment (after one repeat determination) to the appropriate clinic. This action was recorded in the individual's chart as a part of the permanent record. If the abnormality was considered to be related to the work hazard, the necessary steps, as indicated, to safeguard the individual's health were taken and the progress of the anemia followed.

C. Platelet Counts (direct Sodium Citrate method) and other procedures used in evaluating blood coagulation

For practical purposes it was considered that the platelet values of the peripheral blood of personnel would be affected in a manner comparable to the leucocytes per cu mm after an acute or chronic exposure to externally originating ionizing radiation.

Platelet determinations were performed on selected work hazard groups and a suitable number of controls. Routine determinations on all personnel were not instituted. The normal limits were considered to be 275,000 +/- 100,000 per cu mm. If values below the minimum were discovered, repeat determinations were made at intervals described under Leucocytes in A. A careful investigation of the work hazard was made and further disposition of the case depended thereon. Values above 375,000 persisting on one repeat determination were considered specially as they arose and no definite routine established. In special cases prothrombin time, bleeding and clotting time, and capillary fragility were instituted.

D. Sedimentation rate

Sedimentation rates (Wintrobe and Westergren) were determined on all new

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employees but not instituted as a routine procedure. Studies were confined to specially designated control and work hazard groups. The frequency of this laboratory examination in such specially designated groups depended upon the frequency with which other hematological studies were conducted.

E. Urine examinations

Routine urine examinations were made on the control group at intervals of six months after the initial pre-employment study. If abnormalities were found, the examination was repeated at intervals of one week for three consecutive weeks. A persistent abnormality was reported to the individual involved and he or she referred to the proper clinic. This disposition and result of investigation was made a part of the individual's permanent project health record.

Individuals who were working with hazardous or potentially hazardous materials such as uranium which might produce kidney damage had repeat urine determination at regular intervals. Abnormalities found and throught to be due to the work hazard served as an indication for more frequent examinations and the disposition of such a case depended upon the Liaison Committee's investigation and recommendations.

V. A Liaison Committee

A committee which was composed of the Director of Health, the Chief Industrial Physician, the Chief of Clinical Laboratories, and the Chief of the Health Physicists and their respective strategic assistants met regularly at least once weekly. The function of this committee was to review the activities of the laboratory in terms of the industrial hazards. A report was given by the health physicist which included the data on personnel and area monitoring for the previous week. Thus, the degree of individual exposure to radiations, to uranium, etc., and the general level of laboratory contamination with these materials was brought up for consideration. If, from this report, a research laboratory showed a mounting contamination in terms of uranium hazard or contamination with other radioactive materials, decisions were made to close operation in the particular laboratory for decontamination and recommendations made to reduce the likelihood of a repetition of the condition. A report on all clinical

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laboratory abnormalities was submitted by one of the physicians. Their abnormalities were then considered in terms of the type and degree of work hazard exposure the particular individual had sustained in the past and a decision made which was considered to be in the best interests of the individual's health.

VI. Clinical Laboratory Abnormalities Encountered

The number and variety of abnormalities found during a typical month of operation at the Metallurgical Laboratory in Chicago is shown below in Table I. Scrutiny of this Table will reveal the many clinical problems involved in reaching appropriate conclusions as to the part played by the work hazard in the abnormalities encountered. For example, if a leucocyte count on an individual was found to be below 3000 per cu mm, it was immediately checked by calling the individual back to the clinical laboratory for a repeat determination. His previous hematological record was available for study and if the date indicated a drastic reduction had occurred, it was necessary to determine whether the abnormality was secondary to a coincidental infection or other origin, or actually related to the physical hazard encountered in working with a radiation source or sources. The individual was occasionally of necessity subjected to careful questioning concerning his work activity, his present health and a physical examination was frequently necessary. The health physicist investigated the room or rooms in which the individual was working and frequently would reconstruct the previous week or weeks of activity with the help of the individual's immediate supervisor in order to ascertain as nearly as possible the amount of radiation exposure involved. When "film badges" and "ionization chambers" were worn by workers after these became available in sufficient quantity, the approximate amount of external radiation accumulated by an individual for any period was known. Such records on an individual obviously made a decision as to the part played by radiation in such a leucopenia much simpler. The need for careful interrogation of personnel and physical examination in suspected cases which developed leucopenias is illustrated by the following incident which was one of many related incidents. As pointed out above, certain research groups who were working intimately with large radiation sources such as fission products or in the vicinity of an experimental "pile" had hematological

1194

TABLE I

All abnormalities of urine, including presence of: Albumin Reduction Casts, wbc, rbc, etc.	Erythrocytes per cu mm below Male 5.5 x 10⁶ = 1.0 Female 5.0 x 10⁶ = 1.0	Hemoglobins below Male 16 gm/100 cc = 2 Female 14 gm/100 cc = 2	Poly-lymph-reversal	Leukocytes - below 5000/ cu mm	Leukocytes - above 10,000/cu mm	Lymphocytes - below 1500/cu mm	Lymphocytes - above 3400/ cu mm	Neutrophils - below 2500/cu mm	Neutrophils - above 7400/cu mm	Monocytes - above 6 per cent	Eosinophils - above 5 per cent	Immature leukocytes	Platelets - below 175,000/cu mm
149	105	146	86	62	94	37	140	45	54	74	42	15	32

The number of individuals with clinical laboratory abnormalities of various kinds during the month of March 15 - April 15, 1944. Total number of individuals examined during this period was 1228. These numbers include individuals in both the control and work hazard groups.

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studies at frequent intervals, once to twice weekly in certain cases. This seemed indicated since it was not unlikely that large acute exposures could be sustained. Several individuals in one such group were found to have leucopenias of less than 3500 on one particular examination. Their previous leucocyte value had been 5000 or over. Immediate investigation of the individuals concerned indicated they probably had early German measles. The subsequent observation proved this to be true. In other instances it was not possible to relate leucopenias to infection or indeed to any ascertainable etiology. Even if results of the survey of the work area for possible radiation exposure indicated essentially insignificant findings, the question of chance overexposure due to carelessness or utter disregard for caution on the part of the individual had to be considered. If it seemed warranted, the individual was removed from all possible chance of radiation exposure and observed carefully from a hematological and clinical standpoint. The practice of shifting workers from areas of high radiation exposure or potentially high exposure areas to work areas wherein negligible amounts of radiation exposure was possible, and was not uncommonly done, if laboratory findings warranted caution.

VII. Studies Made on Individuals with Leucopenia

Except for purposes of control, studies were not made on those individuals whose leucopenia was attributable to infection or other known cause. These studies were carried out on only those individuals with leucocyte values below 4800 per cu mm.

A. <u>Effect of exercise on the number of leucocytes of the peripheral blood</u>

Thirty-five individuals with leucocyte values of from 4800 to 3150 per cu mm were subjected to the "standing running exercise" for one minute during which time the individual exerted himself to the utmost and raised his feet above the floor at least twelve inches. Individuals with normal leucocyte values were subjected to the same test for comparative purposes. A control leucocyte count and differential smear were taken immediately before the exercise was begun and immediately after it was completed. Another sample was taken fifteen minutes after completion of the exercise. In all individuals so examined immediately after exercise an increase in the leucocyte value occurred. Several of these

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cases are illustrated in Table II. The average increase was 36.2 per cent (lowest 5.9 per cent and the highest 75 per cent). The increase was primarily an increase in the polymorphonuclear neutrophil leucocytes. No shift in the stage of maturation of these mobilized cells was apparent. The fact that exercise affects an increase in the leucocyte value has been reported by Bryan, et al(10), Schneider and Havens(11), Zeller(12), Granwitz(13), and many others. The increase represents mobilization of leucocytes and does not necessarily indicate the functional state of the hemopoietic tissue. No correlation exists between the type of response to the "exercise test" and degree of exposure to radiation. Individuals on the project who had developed a leucopenia, the etiology of which was unknown, responded to infections such as upper respiratory infections and other minor infections by increases of as much as 100 per cent or more in the leucocyte value.

B. Variation of total leucocyte values during one day

Leucocyte and differential counts were made on a number of individuals with a leucopenia at 8:30 A. M., 11:00 A. M., and 4:00 P. M. Results of these determinations are shown in Table III. Seventy-one and a half per cent showed an increase at the 4:00 P. M. determination, 16.6 per cent remained essentially the same and 11.9 per cent showed a slight further decrease. Forty per cent of the leucocyte counts remained essentially unchanged at the 11:00 A. M. determination; 25 per cent were slightly decreased and 35 per cent were slightly increased. Ponder, et al(14), Sabin, Cunningham, et al(15), and Shaw(16) have studied the diurnal variation in the leucocyte values of normal individuals and reported inconsistent but frequent increases in the afternoon sampling. No particular value of a practical nature could be assigned to the results we obtained in studying these individuals except that a relatively normal diurnal fluctuation was obtained. The fact that certain individuals failed to respond with an increased leucocyte value could not be correlated with an increased exposure to ionizing radiation.

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TABLE II

Control

	WBC	Polys		Lymphs		Mon.	Eos.	Bas.
		%	per cu mm	%	per cu mm			
Before exercise	4200	59	2478	31	3780	8	2	0
Immediately after	6350	48	3048	48	3048	2	1	1
15 minutes later	2950	55	3272	38	2261	4	2	1

Polynuclear lobe count

Lobes	1	2	3	4	5	total per 100 neutrophils
Before exercise	10	46	38	6		240
Immediately after	14	40	36	10		242
15 minutes later	9	49	31	11		244

Work Hazard

	WBC	Polys		Lymphs		Mon.	Eos.	Bas.
		%	per cu mm	%	per cu mm			
Before exercise	3950	50	1975	40	1580	7	2	1
Immediately after	6900	50	3450	44	3036	4	1	1
15 minutes later	4300	48	2064	39	1677	8	3	2

Polynuclear lobe count

Lobes	1	2	3	4	5	total per 100 neutrophils
Before exercise	1	38	44	15	2	279
Immediately after	2	36	42	19	1	281
15 minutes after	2	50	37	11	0	257

The effect of exercise on the leucocytes per cu mm and differential leucocytes of control and work hazard personnel.

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TABLE III

Control

	WBC	Polys %	Polys per cu mm	Lymphs %	Lymphs per cu mm	Mon.	Eos.	Bas.
8:30 A. M.	4000	50	2000	40	1600	7	3	0
11:00 A. M.	4050	48	1944	38	1539	8	5	1
4:00 P. M.	5100	42	2142	48	2448	7	3	0

Work Hazard

	WBC	Polys %	Polys per cu mm	Lymphs %	Lymphs per cu mm	Mon.	Eos.	Bas.
8:30 A. M.	3900	56	2212	33	1203	3	7	0
11:00 A. M.	3900	58	2262	32	1248	5	4	0
4:00 P. M.	5050	55	2277	34	1717	6	4	2

Daily variation in leucocyte and differential values of individuals with leucocyte values of 4800 or below.

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C. Effect of adrenalin injections on the leucocyte values of the peripheral blood

The use of adrenalin injection or related substances to study the response of individuals with leucopenia likewise is probably of little practical value in assessing the functional state of the hemopoietic system; nor in our experience can the response to such stimulation be correlated with the degree of chronic radiation exposure sustained by an individual. As is already known, the presence of a leucopenia in animals caused by chronic gamma ray exposure does not prevent remarkable increases in the leucocytes of the peripheral blood with infection, Lorenz, Jacobson, et al[17]. Likewise, positive increases in leucocyte values in individuals after adrenalin injection does not preclude the possibility that the individual has sustained a relatively high chronic exposure to ionizing radiation. Lucia, Leonard, and Falconer[18], Martin[19], Hoff[20], and others have reported the relatively rapid onset of leucocytosis in normal human subjects subsequent to adrenalin injection. The effect of adrenalin injection on a young negro project scientist with a leucocyte count of 4100 per cu mm is illustrated in Figure I. Leucocyte and differential counts were made immediately before the subcutaneous injection and at 1/2 hour intervals thereafter for 2 1/2 hours. The leucocyte value is increased circa 56 per cent by thirty minutes after injection and gradually fell thereafter. The polymorphonuclear neutrophils increased during the 2 1/2 hour period of observation while the lymphocytes rose abruptly reaching a maximum 1/2 hour after injection and then gradually fell to a value below the pre-injection control.

D. Sternal bone marrow aspiration studies

Sternal aspirations were performed on individuals working in areas of relatively high exposure to radiation who had developed a leucopenia and in individuals of the "control group" who had leucopenias. The results in both groups were normal and essentially similar. No evidence of abnormal morphology of the various precursors or evidence of maturation arrest was encountered. A typical example of bone marrow aspiration findings is given in Table IV. This individual

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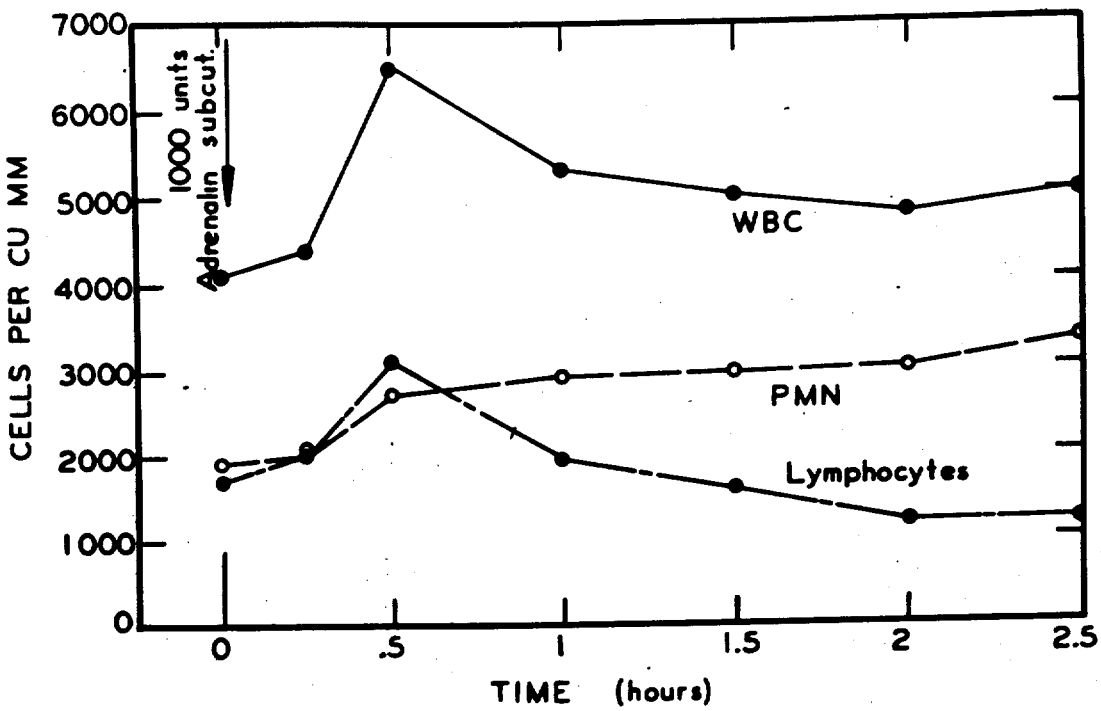
7000
6000
5000
4000
3000
2000
1000
0
CELLS PER CU MM
1000 units
Adrenalin subcut.
WBC
PMN
Lymphocytes
0
.5
1
1.5
2
2.5
TIME (hours)

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TABLE IV

Bone Marrow Date 9/29/45

	Per cent
Myeloblasts	0.5
Promyelocytes	0.5
Myelocytes: Neutrophilic	11.0
Eosinophilic	1.0
Basophilic	0.5
Metamyelocytes	15.0
Polymorphonuclear neutrophils	18.0
Polymorphonuclear eosinophils	0.5
Polymorphonuclear stabs	17.0
Lymphocytes	10.0
Proerythroblasts	1.0
Basophilic erythroblasts	5.0
Polychromatophilic erythroblasts	9.0
Normoblasts	11.0
1000 cells counted	

The per cent of various cells found on study of the bone marrow of Q. V. The leucocytes per mm cu in the peripheral blood of this individual numbered 3100.

1119469

has a persistent leucocyte value of 3300 which developed while working with but not necessarily related to radiation sources. As reported by Lorenz, et al[17], the bone marrow of mice exposed chronically to 4.4 r for eight hours per day for a period of more than two years may be essentially normal on histological examination.

E. Morphological studies

Morphological studies of the erythrocyte and nucleated constituents of the peripheral blood conducted on work hazard and control groups failed to indicate changes attributable to radiation exposure. Cooke and Ponder's modification[21] of the Arneth count was used to determine whether a shift to the left of the polymorphonuclear cells had occurred in laboratory personnel as a result of exposure to radioactive materials. The results were recorded in terms of the total lobe count according to Hargraves[22] and are seen in Figure II. The total lobe count of work hazard personnel varied little from that of personnel from the control groups. The polymorphonuclear shift to the left which is described following radiation, occurs only after prolonged heavy exposure or after single acute doses. Simon[23], Bayer[24], Coke and Ponder[21], Isaacs[25], Jacobson[26]. In certain of the work hazard groups in which the radiation exposure was considered to be relatively higher than other groups, supravital staining of the leucocytes with Janus green and neutral red was undertaken. No increase in neutral red granules in the lymphocyte cytoplasm was observed. Isaacs[25] reported an increase in the neutral red granules of the mononuclear cells of the peripheral blood of the human after therapeutic x-radiation. We have likewise found such an increase in the human after exposure to total body x-radiation in divided doses totaling 50 r given in a six-day period. In rabbits the neutral red granules of the lymphocytes of the peripheral blood are increased after exposure to 200 r total body x-radiation and above when given in one acute dose.

F. Daily leucocyte counts conducted for more than one year

Daily total leucocyte and differential blood counts were done on four

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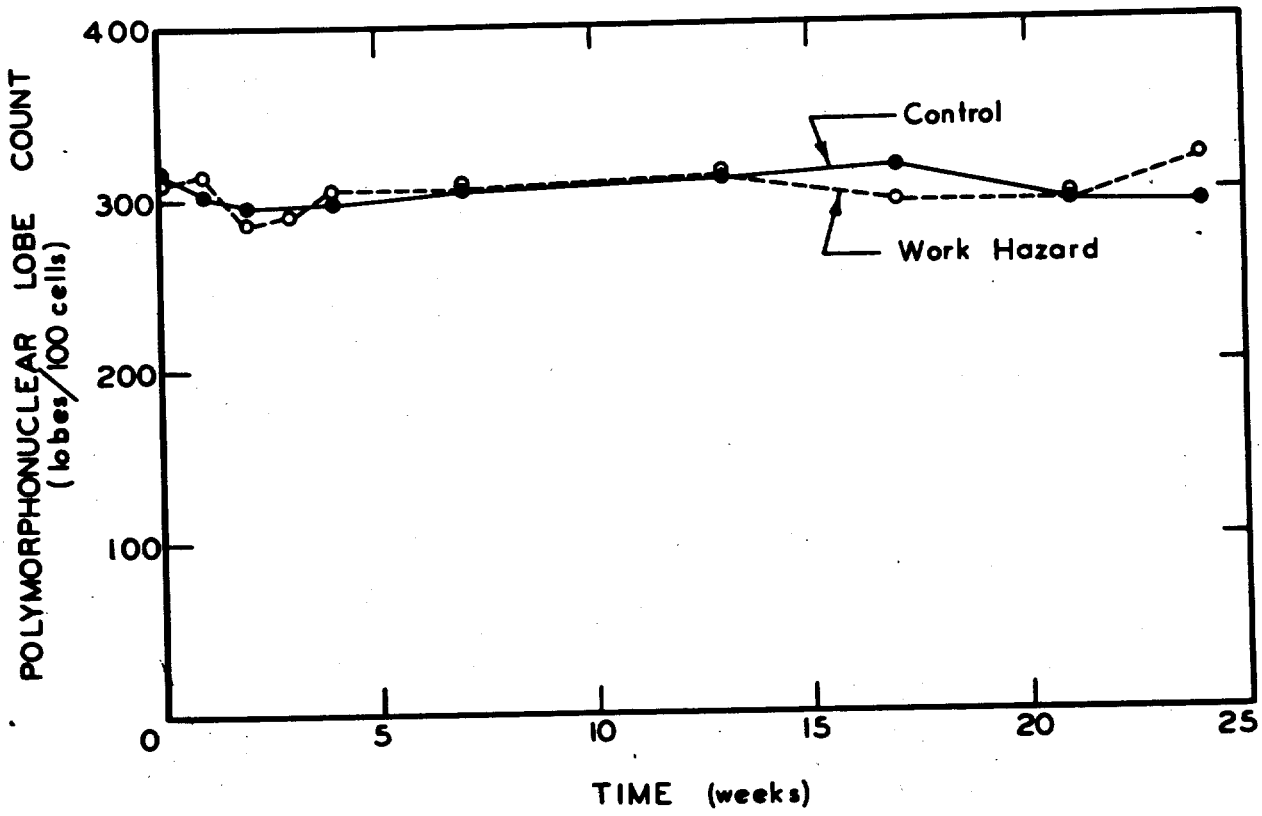
400
300
200
100
0
5
10
15
20
25
POLYMORPHONUCLEAR LOBE COUNT
(lobes/100 cells)
TIME (weeks)
Control
Work Hazard

1119471

laboratory workers approximately the same time each day (9:00 A. M.) for a period of more than one year. Reticulocytes, hemoglobin and erythrocyte determinations were also done but at less frequent intervals. These cases will be reported in detail elsewhere[27]. Values based on the average of one month periods during the year are given in Table Va and Vb. No significant seasonal variations were noted nor were there any other variations of magnitude which were not attributable to infections, such as respiratory infection, etc. This study indicated the important practical fact that normal individuals maintain a relatively constant leucocyte value from day to day and month to month, unless disturbed by infection, pregnancy and the like. Shaw[28] is the only author who reports leucocyte counts taken daily over a period of one year to our knowledge.

VIII. Evaluation of Clinical Laboratory Studies Conducted on the Plutonium Project

A. Urine Studies

Very early in the history of project research and operation it became apparent that exposure to the uranium isotopes either in terms of contact with the skin, inhalation, or ingestion(except for the fluoride and other compounds which similarly have chemically toxic elements in the molecule) did not alter the urine of personnel to the extent that the study of specific gravity, presence of albumin or reducing substances, casts, or hematuria indicated overexposure. The value of urine studies of this variety was confined principally to the discovery of acute or chronic disease of the urinary tract unrelated to the hazards peculiar to the project. It must be emphasized, however, that studies of the urine were of inestimable value in determining the degree of exposure to uranium and plutonium as the urine is the principal route of excretion of these materials, Tannenbaum[1]. Flurometric analysis of the urine for uranium, Price, et al[29] and radiochemical analysis of the urine for plutonium, Russell, et al[30] made it possible to estimate with a fair degree of accuracy the actual amount of these radioactive isotopes deposited within the body of exposed personnel. Increased porphyrin excretion in the urine was affected by the deposition of uranium in the body of personnel, Ferretti, et al[2].

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TABLE Ia

Average Monthly Count

Subject: [redacted], Male Age-29

Date Month, year	Absolute Neutrophil	Absolute Lymph.	Absolute Mono.	Absolute Eos.
2/45	2867*	2053*	333*	293*
3/45	2945	2155	232	314
4/45	2620	2184	260	248
5/45	3367	2050	271	263
6/45	2768	1880	308	320
7/45	2791	2095	236	364
8/45	2892	2142	319	338
9/45	2705	2005	330	400
10/45	3548	1926	352	400
11/45	2737	2063	369	369
12/45	3090	2095	465	605
1/46	3554	2025	337	450
2/46	2848	2268	404	472
3/46	2900	2291	414	341
4/46	2618	2245	327	327
5/46	2513	2025	379	304
6/46	2750	2550	319	287
7/46	2733	2357	276	271

* per cu mm

Daily leucocyte values of an individual taken over a period of more than one year. Values for each month are averaged in this table for the sake of brevity.

TABLE Vb

Average Monthly Count

Subject: [redacted] Male Age-22

Date Month, year	Absolute Neutrophil	Absolute Lymph.	Absolute Mono.	Absolute Eos.
12/44	2900*	1656*	320*	72*
1/45	2548	1622	255	19
2/45	2452	1674	191	26
3/45	2878	1583	269	22
4/45	3021	1864	300	50
5/45	3146	1708	283	46
6/45	3204	1752	261	48
7/45	3312	1580	268	36
8/45	3411	1623	242	69
9/45	3513	1417	339	74
10/45	3360	1528	300	76
11/45	3209	1573	286	86
12/45	3075	1800	267	67
1/46	3400	1929	288	76
2/46	3250	1813	294	69
3/46	3223	1592	246	15

* per cu mm

Daily leucocyte values of an individual taken over a period of more than one year. Values for each month are averaged in this table for the sake of brevity.

B. Hematological studies of the peripheral blood

On the plutonium project part of the Manhattan district undertaking, relatively few instances were encountered in which changes in the hematological constituents of the peripheral blood of personnel could be attributed to contact with external sources of radiation or the deposition of radioactive materials within the body. The great variation in the steady state of the various hematological constituents of the peripheral blood from one individual to another, the inaccuracy of modern methods for measuring these constituents and the individual physiological variation from hour to hour, day to day, and month to month, make it almost impossible to interpret minor fluctuations resulting from acute or chronic radiation exposure. In animal experiments involving many animals, a known exposure and comparable controls, statistical significance may be attributed to what would ordinarily be considered a minor reduction in the lymphocyte value. If a single animal of the experimental group is compared to the control group, however, it is impossible to attach significance to a minor lymphocyte reduction. Elsewhere in these volumes a statistical study of the variations in the hematological constituents of the peripheral blood in control and work hazard groups of various ages will be dealt with in detail, Sacher, et al(31). No significant alterations were found in these latter studies which were attributable to radiation exposure.

IX. General Remarks

More emphasis on basic biological research on the mechanism of action of ionizing radiations is obviously required before one can logically devise clinically applicable tests to determine and evaluate incipient damage from these agents. This likewise applies to the problem of uranium toxicity. The discovery that a leucopenia, anemia or thrombocytopenia has developed in personnel as a result of chronic exposure to radiation, or that liver or kidney damage is apparent after chronic exposure to uranium, is a discovery of significant damage already sustained, and serves to indicate the inadequacy of our present methods of diagnosis. The concept that no amount of ionizing radiation can be safely tolerated by the human, obviously cannot

1119475

be accepted if work is to continue in this field, but a firm biological basis for a permissable dose should be established. A number of biological investigations which have been carried on in the metallurgical laboratory have practical clinical significance and important fundamental implications. Space does not permit discussion and evaluation of all these studies and only a few are given below.

A. Experiments on the effect of ionizing radiation on coagulation of blood

A prolonged bleeding time, increased capillary fragility, thrombocytopenia and prolonged clotting time have been described following heavy acute exposure of animals to x-radiation Shouse, Warren, and Whipple[32] and have been confirmed in our laboratory, Jacobson, et al[26]. The explanation for a prolonged bleeding time is considered to be related to the thrombocytopenia; neither the increased capillary fragility nor the prolonged clotting time have been adequately explained. Allen, et al[33] working with dogs has shown in our laboratories that this increased clotting time is related definitely to an increase in the amount of circulating heparin and is a major cause of death. It may be sufficient in certain dogs to render the blood incoagulable in the test tube. The anti-coagulant present in the blood of some of these animals is sufficient to alter the coagulability of the blood of normal animals in the test tube. This hemorrhagic state can be repeatedly reversed for varying periods of time (24 to 72 hours) by the administration of purified toluidine blue, protamines and certain of the thionin dyes. The explanation for the hyperheparanemia is not entirely clear but may be related to Clostridium Perfringens or other infections. The practical importance of this work lies in the fact that it represents a definite contribution in treatment of acute radiation injury in man. It is already evident in our own experience on the project that the clotting time may be increased as a result of acute overexposure to ionizing radiation. It seems quite evident from the work of Prosser, et al[34], Zirkle, et al[35], Jacobson, et al[36], Brues, et al[37a,b,c], and Lorenz, et al[17] that the death of animals after acute exposure to ionizing radiation such as X rays and fast neutrons is more frequently due to a cumulative effect of derangement in

1119476

several organ systems rather than one single system failure such as the hemopoietic system. Thus, death may be due to initial shock (rabbits) within the first twenty-four hours, overwhelming infection with failure of immune mechanisms including severe lymphopenia and neutropenia (dog, rabbit) or intractable hemorrhage due to hyperheparanemia (dog). Ability to treat adequately and successfully any one of these or other physiological breakdowns is a step forward.

B. Chronic daily exposure of animals to whole body gamma ray in the "tolerance range"

It was pointed out in the Introduction that prior to the war no truly biological basis for the "accepted human tolerance dose" or 0.1 r per day for indefinite periods existed. An adequate human experiment properly controlled in which this tolerance value could be tested is largely impossible and with this in mind Lorenz, et al[17] set up a number of experiments in which mice, rabbits, and guinea pigs were exposed at a dose rate of 0.01, 0.1, 1.1, 2.2, 4.4, and 8.8 r for eight hours per day and some other experiments where the same dose rate was given for twenty-four hours per day. The radiation source was a gram of radium. These animals were observed while thus exposed over periods extending beyond three years. Significant effects on the hemopoietic system were not reflected in the peripheral blood in any of the three species chronically exposed to doses of 0.11 r per day during more than 3 years of exposure. Chronic exposure to 1.1 r per day and above produced hematological changes in the peripheral blood. The severity of the effect upon the peripheral blood varied with the species; guinea pigs were most sensitive, mice intermediate and rabbits relatively resistant. Of great significance even though direct extrapolation to the human cannot be made is the fact that a statistically significant increase in ovarian tumors appeared at an earlier age in mice exposed to 0.11 r daily to a total accumulated dose of approximately 100 r. As pointed out by Lorenz, et al[17], this fact should perhaps be taken into consideration when women are engaged in radiation work.

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C. Exposure of humans to single and divided doses of externally originating radiation (X ray--whole body)

It was pointed out in the Introduction that few studies had been made on human subjects in which whole body exposure to single or divided (acute and subacute) doses of x-radiation was used. In those studies which were reported the subjects were often too ill as a result of the primary disease process being treated and thus interpretations of the hematological data were difficult if not impossible. Low-Beer and Stone(38) undertook treatment of a number of patients with chronic degenerative disease of the joints with whole body exposure to X ray. The total doses administered varied from 100 to 320 r given daily in divided doses of 5 to 20 r (on the skin). The daily treatment required only a relatively few minutes of exposure. Jacobson and Lick(39) undertook comparable studies. These studies indicated a sensitivity of the hemopoietic system comparable to the guinea pigs, Lorenz, et al(17) and dogs, Prosser and Jacobson(34), Allen, et al(33). With total accumulated doses of 150 r (tissue dose) leucopenia, lymphopenia occurred--the severity, however, varying widely from indiviaual to indiviaual. A striking effect was the definite macrocytic anemia which developed in about 200 days in practically all cases exposed to total doses of this magnitude. Spontaneous recovery of the hematological constituents of the peripheral blood of these individuals was universal but the time required for recovery varied widely.

D. The biological effects of long-lived radioactive fission isotopes

Brues, Lisco, and Finkle(37), Jacobson, et al(40), Prosser, et al(41), Hamilton(42), and Bloom, et al(43) studied a number of representative radioactive fission product isotopes in terms of their distribution and localization, excretion and biological effects in the experimental animals and the human. It is apparent from these studies that once plutonium gains entrance to the body of the experimental animal or the human it is localized largely in bone and is excreted very slowly. Like strontium^{89} and radium it produces bone tumors (osteogenic sarcoma). The effect of those radioactive isotopes liberated in the fission reaction which localize primarily in bone, produce significant

1194 18

adverse effects upon the hemopoietic system; lymphomas and leukemias are common, the smallest dose which will produce a chronic lymphopenia is very near the tumor producing dose. In general, however, it is true that histopathological changes in organs or tissues may occur as a result of the action of these isotopes in the absence of or prior to observable changes in the hematological constituents of the peripheral blood.

X. Summary

The general inadequacy of the routine clinical laboratory examinations such as blood and urine studies in the detection of chronic radiation or uranium exposure in the tolerance range has become evident by our experience on the plutonium project. Extensive hematological and urine studies at frequent intervals were conducted on project personnel (control and work hazard groups) for at least four purposes; (1) to provide a constant check for chance acute overexposure to these agents, (2) to discover any incipient damage to the hemopoietic system or urinary system from these agents, (3) to provide legal protection for the contractor and (4) to keep up morale of laboratory personnel. It was widely known to physicists and chemists that radiation and uranium were toxic to the hemopoietic system and urinary system respectively. The fact that frequent examinations of the blood and urine were being done gave the workers confidence that, in addition to the frequent physical monitoring of work areas and personnel for radiation hazards, the function of their "most sensitive" organ systems was being constantly scrutinized.

Only in relatively few instances did clinical laboratory evidence provide a clear-cut indication that an acute or a chronic radiation exposure sustained by personnel had been excessive. The great individual variation in the steady state of the various hematological constituents of the peripheral blood and the multiplicity of factors which may adversely alter this steady state, temporarily or more chronically, made interpretation of minor variations difficult and often impossible.

The need for more carefully controlled basic studies on the biological effect of physical and chemical agents such as radiation and uranium is stressed. Tests for incipient damage and the establishment of a sound "permissible dose" of radiation or uranium depend thereon.

1119479

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1119482