Title
THE EFFECTS OF ROUTINE OCCUPATIONAL RADIATION EXPOSURE IN WORKERS AT THE LAWRENCE RADIATION LABORATORY, BERKELEY

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Publication Date
1967-05-01

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Berkeley, California

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UCRL-17573

UNIVERSITY OF CALIFORNIA

Lawrence Radiation Laboratory
Berkeley, California

AEC Contract No. W 7405-eng 48

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George Douglas Barr

(Ph. D. Thesis)

May 1967

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The Effects of Routine Occupational Radiation Exposure in Workers at the Lawrence Radiation Laboratory, Berkeley.

Abstract

George Douglas Barr

The hypothesis that there are no physiological effects from routine occupational radiation exposure has been tested in a group of 105 Lawrence Radiation Laboratory (Berkeley) employees. Routine in-plant medical examination results (emphasizing hematology) were compared over a ten-year period with accumulated radiation doses which were taken from film badge records. The range of individual ten-year accumulated radiation doses was 3 to 87 rems. The study hypothesis was not rejected for any medical examination procedure tested, i.e., there were no effects of radiation exposure shown in this investigation.

Approved

Chairman, Dissertation Committee

ACKNOWLEDGMENTS

This study of the effects of occupational radiation exposure was made possible by the assistance and cooperation which I received from all persons concerned.

I want to thank all of the many individuals at the Lawrence Radiation Laboratory at Berkeley who willingly allowed me access to record files and who gave me much assistance in the use of facilities. I am very grateful to Dr. Howard Parker and the staff of the Medical Services Department, to Mr. H.W. Patterson and the staff of the Health Physics Department, and to Dr. John Suttle and the staff of the Personnel Department. In particular, I wish to acknowledge the continued and invaluable support which I have received from Dr. Hardin Jones at Donner Laboratory.

I am very much in debt to many persons at the School of Public Health. Dr. Reuel Stallones in the Epidemiology Department gave me a great deal of advice and encouragement. Mr. William Larkins and the staff of the Graphic Arts Department were extremely helpful in preparing figures and tables.

It is a pleasure to express my gratitude to the Division of Radiological Health of the U.S. Public Health Service, particularly for their generous financial support during the course of this research study. I am especially appreciative of the willing cooperation which was given to me by Dr. Russell Pierce of the State Assistance Branch and by Dr. Arthur Wolff of the Research Branch.

INTRODUCTION

The deleterious effects on health of excessive occupational radiation exposure were apparent soon after the discovery of x-rays in 1895 (Failla, 1960). A large number of radiologists and x-ray technicians reported severe skin and soft tissue damage in frequently exposed body areas. By 1920, many of these individuals exhibited cancer of the skin.

Standards for occupational radiation exposure were developed during the 1920's, largely in terms of the so-called "tolerance dose", which was arrived at by comparing conditions of exposure in which workers were or were not injured during a period of several years. The highest exposure level at which injury (usually listed as skin damage) was not seen was considered a "safe" dose, since it was considered that injury, if any, at levels below this was completely repairable.

As experience accumulated during the 1930's and 1940's, some delayed effects of radiation exposure at levels below the "tolerance dose" began to be evident. Some thought that there might be no threshold for radiation damage, particularly with respect to leukemia and other types of cancer. During the 1950's, radiation protection specialists generally adopted the conservative viewpoint that there was no such thing as a "safe" dose of radiation, since any increment of dose, however small, might carry with it some risk of irreparable injury.

In 1954, the concept of the Permissible Dose was announced by the National Committee on Radiation Protection (1957). The Permissible Dose was defined as "...the dose of ionizing radiation that, in the light of present knowledge, is not expected to cause appreciable bodily injury to a person at any time during his lifetime." Radiation doses at the "permissible" level are not considered to be "safe", since there may still be a very small chance of injury. However, at this dose level, the risk of injury is considered to be acceptable, that is, it is small compared to other risks encountered in a working career.

The actual magnitude of the chance of injury at radiation levels near or below the Permissible Dose is not known. Investigations in this area are hampered by the necessity to collect and analyze very large amounts of employee medical data in order to detect small increases in risks.

An effect of the increasing knowledge of human radiobiology has been the stepwise lowering of the standard for occupational radiation exposure from the original "tolerance dose" of 0.1 roentgen (air dose) per day to the present (since 1957) Maximum Permissible Dose for whole-body exposure of 5 rems per year, averaged over all years since age 18. (The word "rem" is an acronym from the words roentgen-equivalent-man. It is a dose unit which is common to all types of radiation).

The present study was designed to provide additional data on the physiological effects in humans of doses near the present Maximum Permissible Dose.

At the present time, there are no satisfactory criteria for medical examination results which will enable the identification of employees who may be showing effects of low-level radiation exposure. The following questions remain to be answered.

1. Do the results of the routine occupational medical examination procedures (hematocrit, leucocyte count, etc.) show any effects of low-level radiation exposure?
2. The results of some special medical examination procedures (cytogenetics, lymphocyte morphology) seem to show some effects of low-level radiation exposure. Are any of these procedures usable in an occupational medical program?
3. What are the shapes of the dose-response curves in low-level radiation exposure? Can dose thresholds be demonstrated for any of the effects?
4. Are any of the reported physiological effects likely to be useful as indicators of effects on health?

Radiation exposure at the level of the present standard is not expected to cause significant changes at any time in the physiological variables usually included in a medical examination. A study of the effects of such exposure must be designed to investigate relatively minor physiological changes. This implies a program of data collection over a period of at least several years, in a fairly large group of subjects, some of whom are exposed at levels near the standard. An attempt should be made to eliminate any effects of possibly interfering variables such as age.

A very important objective of such a study is the establishment of quantitative dose-effect relations. This means that some kind of personal dosimetry must have been available throughout the period of the study for each subject, and that adequate records have been kept of the results.

The following literature review is in terms of the above criteria for studies of the results of occupational radiation exposure.

The procedures involved in abstracting information from medical and dosimetric records are tedious and time-consuming. In a large study population, the volume of the resulting data causes problems in data processing. A number of investigators in this field have attempted to reduce the labor of data collection and processing by selecting only the latest medical records from employees who may have been exposed for relatively long periods. The employees were then sorted into a few groups by relative radiation doses and the medical results were averaged over the groups. The radiation doses may be indicated by a division of the population into "exposed" and "control" groups, often by making assumptions about the relative amounts of radiation exposure associated with occupational classifications. In this type of study, the length of the period of occupational radiation exposure may be specified (Backer, 1958), or not (Moshman, 1951). Radiation exposures may be presented as averages of rates over large groups of individuals with, again, the length of the period of exposure specified (Dickie and Hempelmann, 1947; Pearlman and Sacher, 1951; Turner, 1954; Urushiyama, 1959), or not (Chamberlain, et al., 1952; Fletcher, 1954). There have been no effects of occupational radiation exposure shown in studies of this type, in which data are averaged over large groups of individuals, except in the report by Dickie and Hempelmann, who found a decrease in leucocyte counts of exposed employees.

There are several reasons why studies which proceed by averaging medical and dosimetric data over large groups are not likely to yield positive results. The normal person-to-person and time-to-time variations in the results of routine hematology examinations are so large that it is difficult to establish small differences in results in such a comparison of groups. For instance, Wintrobe (1961) proposes an expected range of leucocyte counts in normal adults of

5,000 to 10,000 cells/mm^3, and remarks that values above 10,000 have been found in 11% of apparently normal adults. The technique of averaging radiation doses over a large group of individuals results in a situation in which any radiation effect in some individuals with relatively high doses may be masked by the general lack of effects in the group. Finally, in industrialized countries most persons experience medical and natural irradiation in varying amounts. The members of a "control" group may have been exposed to less radiation than persons in an "exposed" group, but they are not, strictly speaking, "unexposed." The nature of the human response to low-level irradiation is poorly understood. In a group study, some members of the "unexposed" group may be showing a response to non-occupational irradiation, confusing the comparison with the "exposed" group.

Considering all of the objections, it is interesting that Dickie and Hempelmann were able to demonstrate an effect of occupational radiation exposure in the group study of cyclotron workers which was mentioned above. They reported average doses in their exposure groups in terms of "up to" 1 to 3 roentgens per month, at a daily rate of "up to" 0.1 to 0.5 roentgens, over a total period of two years. These dose rates would lead to yearly rates of up to 10 to 40 roentgens, a dose which is considerably higher than the present standard of 5 rems per year (assuming equivalence of dose units). If a fairly high proportion of the exposed group was irradiated at near the maximum level reported, then the group generally had a high dose relative to present standards, so that some effects might be seen in the results of routine hematology examinations, even though the data were averaged over groups of individuals.

The report by Dickie and Hempelmann (1947) also pointed out changes in lymphocyte morphology in the same group of cyclotron workers. This prompted a series of studies of such changes in the hope of developing a medical examination procedure which would yield results which were both specific to radiation exposure and proportional to the dose. In these studies, the results were generally averaged over groups of exposed individuals and dosimetry was sketchy or absent (Dickie and Hempelmann, 1947; Ingram et al., 1952). The only such inquiry in which hematology and dose data were both analyzed in terms of individual employees was published by Dobson and Chupp (1958). They reported an increase in lymphocytes with a specific abnormality in cyclotron workers exposed at rates of 0.1 to 0.2 rems per week. The method is probably not useful as a routine laboratory procedure. Dobson and Chupp mention that the results may not be specific for radiation exposure. The technique is extremely laborious, since it involves counting tens of thousands of lymphocytes in each sample in order to establish the significance of an increase in the extremely small proportion of specifically abnormal lymphocytes in the circulating blood.

The application of cytogenetic techniques to low-level radiation exposure studies offers some promise of relating human biological effects to radiation doses, even at present occupational levels. In a study whose subjects included some workers at the Lawrence Radiation Laboratory at Berkeley, Norman et al. (1964) reported an excess of chromosomes with morphological aberrations in leucocytes from the peripheral blood of 36 persons exposed at a median rate of 1.4 rems per year over a period of several years. Unfortunately, this technique requires a laborious scanning process in scoring frequencies of defective chromosomes in prepared samples. Recent attempts have been made to automate this process, but until they are successful, these cytogenetic techniques are too laborious to be included in a routine occupational medical program.

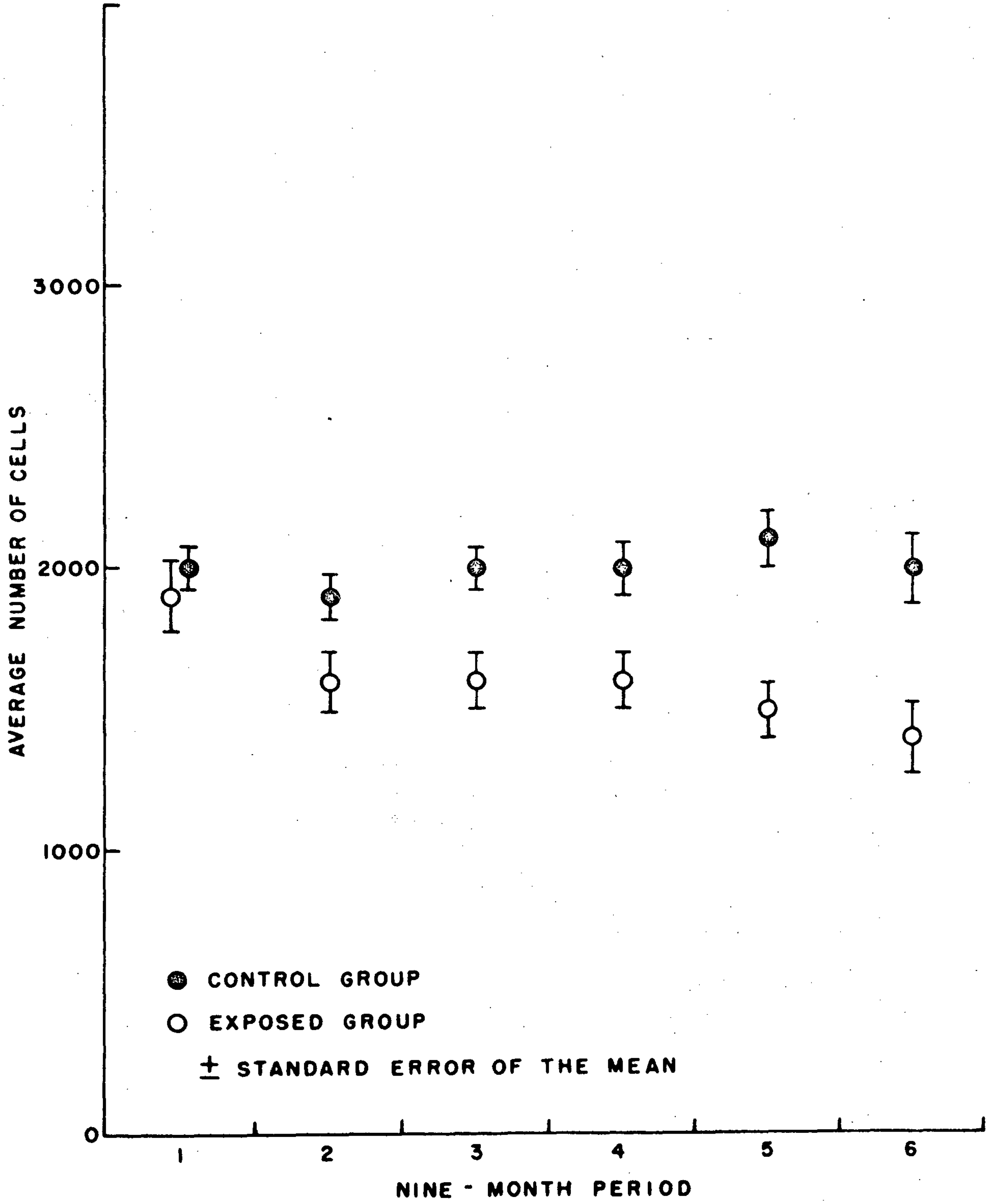
Studies of hematological effects in animals at radiation levels on the order of five roentgens per year are presently lacking. In a report published in 1949, Jacobson, Marks, and Lorenz (1949) concluded that there were no definite hematological effects in small mammals irradiated at a rate of 0.11 roentgens per day over a period of three years.

Assuming equivalence of dose units between species, this is a far higher dose rate than the present occupational standard. The hematological effects of low-level irradiation in animals are probably similar to those in humans, so that careful studies in large experimental populations will be necessary to establish definite results.

One of the few studies of the effects of routine occupational radiation exposure on the blood picture in which the investigators selected a study population according to individual recorded doses was carried out by Knowlton, Carter, and Worman at the Los Alamos Scientific Laboratory. The results were reported in several publications (Knowlton, 1950; Carter and Knowlton, 1950; Carter and Worman, 1952). Blood cell counts were compared in two groups of employees. The "exposed" group consisted of ten persons with radiation exposures over a range of an average of 0.097 to 0.192 roentgens per week, over a total period of 4.5 years. At this rate, the accumulated doses would have been about 50 to 100 roentgens in ten years. The exposed group was compared with a control group of 46 employees in which the average dose level was known to be less than that of the exposed group by at least a factor of ten.

The lymphocyte counts reported by Carter and Worman are presented in Figure 1 (page 10).

Figure 1. The Trend of the Average Lymphocyte Counts Over Time in Workers at the Los Alamos Scientific Laboratory, 1946-1951.



Carter and Worman derived the data points shown in Figure 1 by first averaging the lymphocyte counts for each subject during each nine-month period. Then, for each time period, the mean of the individual subject means was computed, with its standard error. The difference between the means of the two groups was significant at the 0.05 level in all periods after the first one. In the equation which expressed the regression of lymphocyte counts on time in the exposed group, the coefficient was -69.1 cells per mm^3 per 9-month period, which was significant at the 0.01 level. In terms of a ten-year study, the regression coefficient would have been -920 cells per ten-year period. No such trend was seen in the lymphocyte counts in the control group.

The results of the search in the scientific literature for studies of the effects of routine occupational radiation exposure may be summarized as follows. In cases where the average weekly dose is less than 0.1 rem, no definite effects on the blood picture have been seen. In cases where dosimetric records have established dose rates greater than 0.1 rem per week, depressions of leucocyte and lymphocyte counts have been reported. In addition, special techniques have demonstrated chromosomal aberrations in persons irradiated at less than 0.1 rem per week and an excess of cytological abnormalities in persons irradiated at 0.1 to 0.2 rem per week.

Returning to the questions about the effects of occupational radiation exposure which were presented earlier in this section, they may be answered as follows.

1. The leucocyte count and differential leucocyte count are routine occupational medical procedures. They have been found to show effects of radiation exposure, but only in persons irradiated at levels somewhat above the present occupational standard.

2. The results of some special laboratory procedures have shown effects of radiation exposure at levels near the occupational standard. At present, these procedures are too laborious to be useful in a routine occupational medical program.

3. At low irradiation levels, the shapes of the dose-effect relationships with respect to hematological variables are not known. This is a complex picture in which some of the variables are the type and energy of the radiation, the rate of irradiation, and the physiological system being considered.

4. No follow-up studies have been reported of any of the individuals included in the investigations listed above, so that whether any of the reported effects on the blood picture are predictors of effects on health is not known. This is

an important question, and a follow-up study would be useful.

The results reported by Knowlton, Carter, and Worman make it seem likely that other such studies will also produce useful findings if they include persons exposed at levels not far above the present occupational standard. In the present investigation, the study population includes such individuals.

In conclusion, the comments of the United Nations Scientific Committee on the Effects of Atomic Radiation (1962), concerning the need for studies of the effects of low-level irradiation in human beings, are cited. "Laborious though it may be to make observations on the effects of low doses on large human populations, such observations will be invaluable in complementing and confirming extensive animal experiments." "Both clinical, and vital and health statistical studies...of occupationally exposed persons require continued support and prompt reporting."

METHODS

The Study Population

The Lawrence Radiation Laboratory was organized in 1942 to assist in the nuclear warfare program of the U.S. during the Second World War. After the War, the Laboratory rapidly developed into a world-famous center for nuclear physics research. Two very large nuclear particle accelerators, the 184-inch Synchrocyclotron and the Bevatron, were in full operation by 1955. No nuclear reactors have been built at the Laboratory in Berkeley.

The Lawrence Radiation Laboratory presently includes several sites, with major research facilities at Berkeley and Livermore, and smaller ones elsewhere. In this report, "the Laboratory" refers to the one at Berkeley.

Since its inception in 1942, the Laboratory activities have included a large variety of programs in physics, biology, and chemistry. This has resulted in the employment of a wide diversity of employees within the major categories of scientific, craft, and office personnel.

The total number of employees at Berkeley has increased ten-fold since 1942. Starting at a few hundred during the War, the number rose to 1,300 in 1950. By 1960, there were 2,400 employees and at present the number stands at 3,300.

A number of factors were considered in developing the criteria for the selection of the individuals in the study group.

An employee's relative exposure to occupational radiation may be estimated from his occupational classification by assuming, for instance, that persons in technical and scientific categories are more likely to be exposed than those in secretarial and other office jobs (See Turner, 1954). The use of this procedure for sorting employees into "exposed" and "control" groups may be questioned. An employee's current job classification may be a poor guide to former ones, particularly in administrative personnel. In the present study, selection for inclusion in the study group was on the basis of recorded radiation dose, without regard to job classification.

In a population like the Laboratory working force, the members of a "control" group with no recorded radiation exposure may differ in several ways from the members of an "exposed" group, particularly with respect to type of occupation and working conditions. For instance, employees who accumulated significant radiation doses during the period from 1947 to 1955 occasionally worked long and irregular hours while installing and rebuilding the large accelerators. In this study, any bias in medical examination results from such concurrent stresses was minimized by the selection of a study group in which all of the members had recorded radiation doses, but over a wide range, from the level at which blood picture changes were reported in the Los Alamos study, down to a level near the natural radiation environment, at which no biological effects have ever been seen. There was no arbitrary division of the group into "exposed" and "unexposed" subgroups, as is customary in studies of the effects of occupational radiation exposure, but a comparison of medical examination results over a wide and continuous range of doses.

After a pilot study, the following criteria were developed to select a study population whose members would represent a wide range of doses accumulated over a relatively long period of time. From the overall population of all persons who were ever employed by the Laboratory at Berkeley, individuals were chosen who had at least ten years of continuous employment there, as well as recorded radiation doses averaging at least 0.5 rem per year. The procedure was intended to result in a final study population of about 100 persons, representing a collection of medical and dosimetric data which would be large enough to yield useful results within the limits of a feasible study design.

Selection by length of service was carried out by the use of card files in the Personnel Department in which are maintained the name and a limited amount of descriptive data for every person currently or formerly employed by the Laboratory. These files, amounting to about 20,000 cards in all, were searched for the names of all persons who had ever been employed by the Laboratory for at least ten years. This resulted in a list of about 1,000 persons, about 800 of whom were still not terminated in 1965. The final study population was selected from among the employees in this list, according to recorded individual radiation doses.

For each person finally selected, the files were again referred to for his year of birth, year hired, and year terminated (listed as 1965 if still employed).

Dosimetry

Most of the Laboratory activities center around the group of nuclear particle accelerators which are also the main sources of occupational radiation exposure. Many employees assigned to the accelerators receive external gamma and neutron irradiation continuously at low levels during operation of the accelerators and occasionally at higher levels while overhauling them and changing targets. The neutron component of individual doses results from exposure to the accelerators and is usually less than 10% of the total dose.

Significant beta and gamma doses are sometimes incurred by employees handling radioactive materials. In some cases, the material may be accidentally ingested, resulting in internal irradiation.

A number of assumptions were involved in the decision to accept the recorded film badge doses as measurements of the actual employee doses for the purposes of this study.

A general finding in radiobiology is that the extent of the injury from a given dose is likely to be greater if the rate of accumulation of the dose is increased. A study of medical examination results in a group of radiation workers should be more likely to produce useful results if the individual dose rates are fairly constant, so that doses over similar time periods can be compared directly.

Occupational irradiation at the Laboratory is difficult to characterize in terms of dose rates since there are several periodic and intermittent effects involved. The accelerators, which are the main sources of continuous exposure, tend to deliver their output in pulses at rates which range from very high frequencies to the six-second operating cycle of the Bevatron. In addition, employees are occasionally exposed at relatively high rates for a few minutes at a time during such activities as changing targets on the accelerators and handling radioactive materials.

Film badge dosimetry is cumulative in nature and in the resulting designation of the dose as a single quantity, there is no information about any variations in the rate of accumulation during the period of exposure. A preliminary inspection of the records showed that they contained very little definite intelligence regarding dose rates within the film badge periods. Under these conditions, the rate of accumulation of dose by individuals was necessarily assumed to be constant during the data collection period.

The accuracy of film badge dosimetry is sometimes questioned. The relation of the reported film dose to the whole body dose which it is intended to represent may depend on many factors, including the kind of radiation, its energy, and the position of the source with respect to the body, conditions which were continually changing in the employees studied. However, as was explained above, most of the employees included in the study were associated with the accelerators, and their working conditions were generally comparable. The Health Physics Department film badges have been designed to allow for the quality of incident radiation, in order to improve dosimetry. Therefore, the reported doses were accepted as useful estimates of the whole body doses, at least for the purpose of comparing medical examination results among the individuals in this particular study population.

A comparison of employee radiation doses is more difficult if there is a chance that some of the individuals compared have not regularly worn the film badges assigned to them. The usefulness of the film badge program at the Laboratory is generally accepted by the employees. Their degree of compliance with the film badge rules is considered satisfactory by the Health Physics Department. In this study, the badges were assumed to have been worn as scheduled.

The assumption that the employees in the study group had worn their film badges as required was tested. Two long-term supervisors in the group were selected for the test because they were both acquainted with most of the other members of the group. On separate occasions, each of these men was shown the study roster. He was asked if, in his opinion, each person in the roster had been reliable or not in wearing his film badge during the study period. The responses of both supervisors were tabulated.

An inspection of the medical records revealed that some of the study subjects had incurred occupational radiation exposures from sources which were not monitored by the film badge program.

Several persons in the group had accidentally ingested radioactive material in amounts which were not considered to be hazardous, although the material was detected in the excreta. Computing total doses in rems from excretion data is difficult, and in these cases it was considered that the results would not justify the labor involved, since the amounts were small and the data were not complete. Radiation doses from internal emitters were not included in the mathematical analysis.

Some individuals had experienced occupational radiation exposure prior to entering the study, either by working at the Laboratory before the beginning of the film badge program in 1947, or during former employment. The doses from these sources were completely unknown.

Radiation workers are also exposed to radiation from non-occupational sources, including cosmic rays, natural radioactivity, and medical x-ray machines. Doses from these sources were not included in the mathematical analysis. The medical files were found to contain very little information regarding the medical x-ray exposures of individuals. Furthermore, there was no reason to believe that non-occupational radiation exposure was distributed other than randomly with respect to occupational exposure.

In conclusion, the individual radiation doses designated in this study were the combined gamma and neutron doses, as reported by the Health Physics Department. The following assumptions were made.

1. The dose rates of individuals were assumed to be constant during the data collection period.

2. The reported film badge doses were accepted as useful estimates of the whole body doses.

3. The film badges were assumed to have been worn regularly by the employees to whom they were assigned.

4. Radiation doses from non-occupational sources, from internal emitters, and from exposures prior to entrance to the study, were assumed to have no effect on the medical examination results during the period of the study.

The personal film badge dosimetry program at the Laboratory is operated by the Health Physics Department. Members of this group collect the films, develop them, and measure radiation doses from them. Gamma and neutron doses are reported in rems.

The program provides an up-to-date record of the accumulated dose of any employee. It began during 1947 with gamma exposure monitoring. During the early 1950's, the film badge service was extended to include neutron dosimetry. Before 1959, the gamma films were changed each week and the neutron films each two weeks. Both types of films have been changed on a monthly basis since 1959.

All of the original dosimetry records for present and terminated employees have been preserved by the Health Physics Department.

The accumulated occupational radiation dose of each person in the list of ten-year employees was found by searching the film badge record files. In each case, the accumulated gamma and neutron doses were added together to produce a total dose in rems, which was divided by the number of years of employment at the Laboratory to provide an estimate of the average yearly dose.

The individuals found to have average dose rates of at least 0.5 rem per year over the entire period of employment at the Laboratory were included in the original study population of 114 persons.

For each person in the final group, the ten-year radiation dose was determined by summing the gamma and neutron doses recorded during the ten-year period after the beginning of his film badge record. The intent was to record medical and radiation dose data as early in the employee's career as possible in order to use as much data as possible from the 1947-55 period, when doses were relatively high and medical examinations were given relatively frequently. In four cases, most of the dose was accumulated late in the course of an employment period longer than ten years and the ten-year dose was less than 5 rems (less than 0.5 rem per year). These employees were not excluded from the study, since they had met the initial criterion for inclusion of at least 0.5 rem per year over the entire period of employment.

The Medical Examination Results

It was expected that this study would involve a large amount of data and a complex analysis scheme. Some of the medical examination data were included in the analysis to assist in verifying that any radiation effect seen was not merely an artifact generated by the data reduction process itself.

The individual yearly radiation dose rates covered a range from about 0.5 rems, a level at which no radiation effects have been reported, up to about 9 rems, a level at which changes in the blood picture have been seen. This prompted the inclusion of two kinds of medical examination procedures in the mathematical analysis. One category included the hematological tests which might possibly be indicators of radiation exposure at these levels. The other category included medical procedures which were not expected to show any effects of such exposure.

An attempt was made to select medical procedures which were part of the routine physical examination during the entire eighteen-year (1947-1965) data collection period. Over such a length of time, several sources of extraneous variation may affect the results of periodic medical examinations.

Although there were few changes in the techniques of the selected medical procedures during the data collection period, some of the changes may have had unexpected effects on the examination results. Subjects entered the study during all years from 1947 to 1955. The year of entry to the study was included as a variable in the mathematical analysis, in order to minimize any effects of changes in examination methods on the medical data.

Another problem in analyzing medical examination results over a number of years in the same subjects is the possible influence of advancing age. This was controlled by setting the length of time in the study at ten years for all subjects and by including the subject's age at entry to the study as a variable in the mathematical analysis.

All of the blood smear slides for differential leucocyte counts have been preserved. Some selected slides were recounted as a direct test of any changes in technique in this examination.

Any influence of the sex of the subjects on the results was eliminated by restricting the study population to males.

The total data collection period extended over 18 years, from 1947 to 1965. Over a time as long as this, the data may show long-term trends such as those reported by Backer (1958) in hematological data collected in Danish hospital workers during the 21-year period from 1933 to 1954. In the present study, these trends were investigated in two ways. In ten randomly selected members of the study population, the frequency distributions of the leucocyte counts during 1947 to 1954 were compared with those during 1955 to 1964. In all 105 members of the group, the leucocyte count on entrance to the study was compared with the subsequent regression of the leucocyte count on time.

The occupational medical program at the Laboratory is directed by the Medical Services Department. The program has been in continuous operation since 1944.

The routine physical examination includes a chest x-ray and several hematological tests in addition to standard procedures such as body weight, blood pressure, urinalysis, etc. Tests of liver function, bone marrow function, and other special examinations may be made in special individual cases. Copies of the medical examination forms are presented in Appendix A.

The routine medical examination procedures were repeated at different times. All of the procedures were included in the mandatory pre-employment and termination examinations. During the period from 1944 to 1959, the complete physical examination was given at intervals of about eighteen months for each person in the study population. Hematology and urinalysis procedures were scheduled at intervals of three to six months. Since 1959, the frequency of medical examinations has been reduced to once in two to three years for the complete physical examination and once in six to twelve months for the hematology and urinalysis procedures.

The original medical examination forms for all present or terminated employees have been preserved by the Medical Services Department.

The results from sixteen routine medical examination procedures were analyzed for each study subject. Fourteen were hematological tests, including hemoglobin concentration, erythrocyte count, leucocyte count, differential leucocyte count, and occurrence of atypical blood cells. The other two procedures were the determinations of body weight and urine specific gravity, selected because they were simple, objective measurements, frequently repeated, which were not expected to be influenced by radiation exposure at these levels.

The list of medical examination procedures, with techniques, is given in Appendix B. The techniques are standard methods which have remained in use in substantially the same form since 1944, with one exception. Beginning during 1959, the erythrocyte count was made in a flow counter ("Coulter counter") instead of in a counting chamber, and it was dropped as a routine hematological procedure. It was included in the mathematical analysis because it was frequently performed before 1959.

The medical examination data were coded for punched-card data processing according to the directions in Appendix C. Most of the procedures were coded in the original numeric form.

Some conversions were made in the coded medical data on entry to the mathematical analysis. Results which were coded in a "shortened" form (see Appendix C) to save punched-card space were restored to the form originally recorded in the medical file. The differential leucocyte counts were coded in percentages, as in the original record, and were converted to absolute values (cells/mm^3) for analysis.

The medical records were found to be incomplete or missing for nine employees out of the original study group. These employees were dropped from the roster, resulting in a final group of 105 persons.

The Mathematical Analysis

The study was designed to test the hypothesis that there is no physiological effect from routine (low-level) occupational radiation exposure. Statistics were computed in which medical examination results were associated with radiation doses. The hypothesis was rejected or not according to the results of significance tests of the statistics.

A large and complex accumulation of data was expected and a primary objective of the analysis scheme was the expression of the relationships among the study variables in as economical and direct a manner as possible.

The mathematical analysis began with an association in each subject of successive observations of his medical examination results, his radiation dose, and his age. Partial correlation coefficients were computed for each medical examination procedure as related to dose and age. This process was repeated in each of the 105 subjects, resulting in 105 sets of partial correlation coefficients for each medical examination procedure.

For each examination procedure, the hypothesis was tested that the mean of the partial correlation coefficients with dose was equal to zero. Rejection of this hypothesis at the 0.05 level was considered to be evidence for a physiological effect of radiation exposure, leading to rejection of the overall study hypothesis (that there were no physiological effects of radiation exposure).

The mathematical analysis continued with a regression analysis in two steps. The first step was a computation of the trends in medical examination results over time. In the second step, the trends, expressed as regression coefficients, were compared with radiation doses, with allowance for some interfering variables.

In each subject, a measurement was made of the linear regression on time of the results of each medical examination procedure, over a period of ten years. A data matrix was established for each subject in which each column was a specific medical procedure (e.g., body weight), and each row included the results found for all of the procedures on a specific examination date. The regression on time, measured in days from the date on which the subject entered the study, was then determined for each examination procedure. The computation method allowed for missing observations. This process was repeated in each of the 105 subjects, resulting in 105 regression equations for each medical procedure. The coefficients of the equations were entered as data in the second step of the analysis scheme.

As an example, the regression of leucocyte counts on time in a subject may be expressed as

$$Y = a + bX$$

where

Y = the estimated cell count at X days from the date on which the subject entered the study,

a = the estimated cell count on the day of entry,

and b = the average change per day in the cell count. In this equation, b, the regression coefficient, expressed the trend of the leucocyte counts over time as a single quantity, in units of reciprocal days.

The second step of the regression analysis was the association of the trend of the results of each medical procedure with the ten-year radiation dose, both variables having been measured in each of the 105 subjects. A data matrix was established in which the columns were again the medical examination procedures, with three added columns, the subject's radiation dose, his age in years at entry to the study, and his year of entry to the study. In each row of the matrix were the observations made in a specific subject. In the case of the medical procedures, the subject's observations were the regression coefficients which had been computed in the first step of the data analysis. There were 105 rows, one for each subject.

For each medical procedure, the data in the above matrix were entered into a multiple regression analysis. The dependent variable was a subject's regression coefficient (regression on time) computed for that medical procedure. The independent variables were the subject's radiation dose, his age at entry to the study, and his year of entry to the study. There were 105 sets of observations of these variables, one set for each subject. Sixteen multiple regression equations were computed, one for each medical procedure.

The study hypothesis was to be rejected or not for each medical procedure according to the computed significance level of the coefficient in the multiple regression equation which represented the regression of the trend of that procedure on the radiation dose.

To continue the example, the multiple regression equation may be expressed in terms of leucocyte count results as

$$Y = a + b_1X_1 + b_2X_2 + b_3X_3$$

where

Y = the change per day in leucocyte count results at X_1 rems of radiation dose, X_2 years of age at entry to the study, and year X_3 of entry to the study,

a = the change per day in leucocyte count results at zero rems dose, zero years of age at entry, and year zero of entry to the study.

b_1 = the change per day in leucocyte count results per rem of radiation dose,

b_2 = the change per day in leucocyte count results per year of age at entry to the study, and

b_3 = the change per day in leucocyte count results per year of entry to the study.

In this equation, b_1 was the quantity of interest, since it was the regression coefficient which described any effect of the accumulated radiation dose on the trend of medical examination results over time. The study hypothesis was rejected or not for a specific medical procedure according to the results of a significance test of b_1.

All calculations were done by use of the IBM 7094 computer at the University of California (Berkeley) Computer Center. The computer programs for the correlation analysis and the initial regression analysis (regression on time) were prepared by the writer. The computer programs for the multiple regression analysis were COVA and REGRESS in the STATPAK series, a prepared library of statistical computer programs available at the Center. The procedures used in COVA and REGRESS may be found in the program descriptions (Davidson, 1966; Deuel and Iscol, 1966).

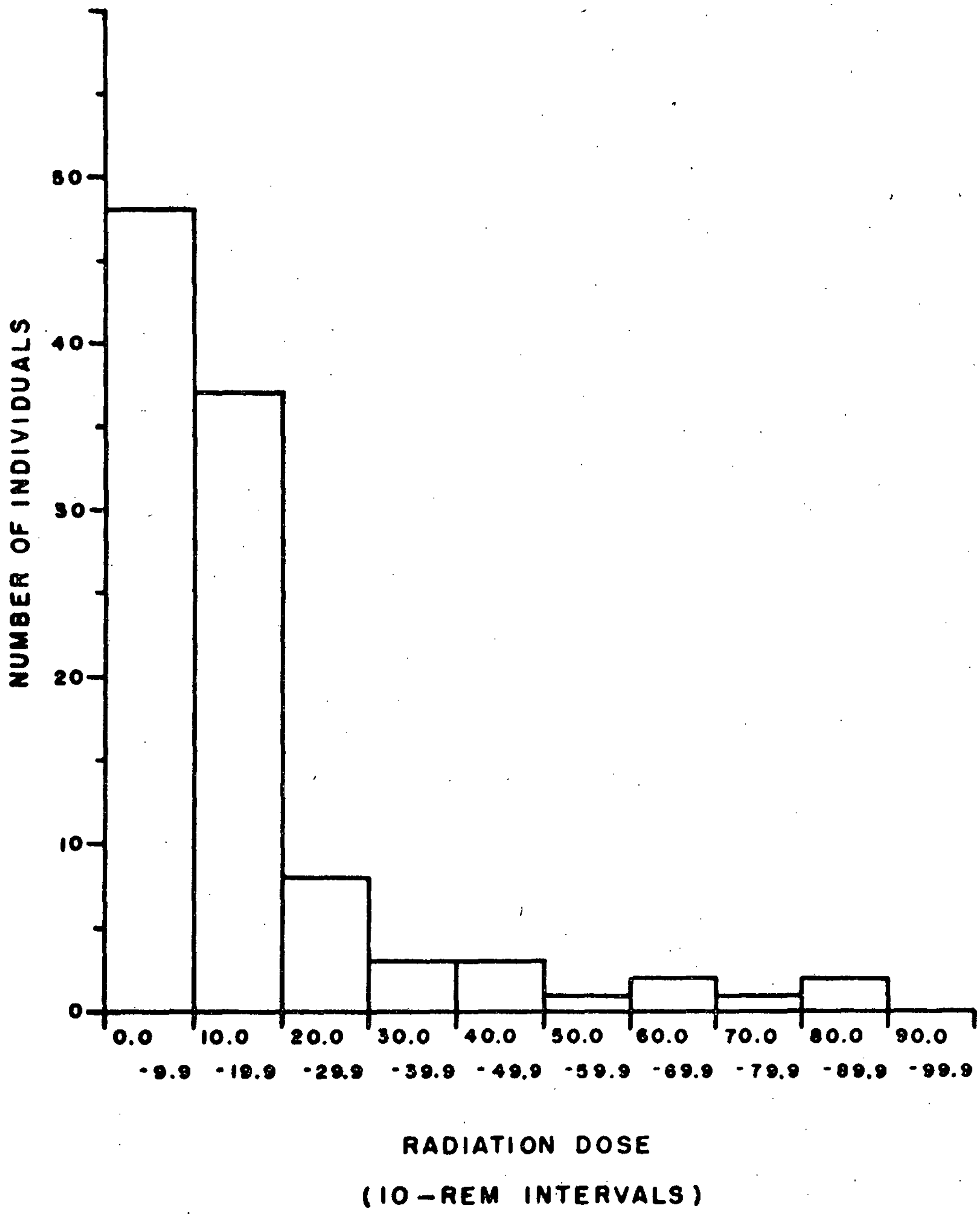
The library programs produced other useful statistics. Correlation coefficients were calculated for all pairs of variables. Frequency distributions, with means and standard deviations, were calculated for all variables. The presentation of each multiple regression equation also included the associated multiple correlation coefficient, the coefficient of multiple determination, and significance tests of the regression coefficients.

RESULTS

Dosimetry

The frequency distribution of the ten-year dose is seen in Figure 2 (page 36), which shows a range of 2.6 to 86.7 rems. The mean dose was only 16.5 rems, which indicated that most of the radiation exposure in this group was at relatively low levels.

Figure 2. The Distribution of the Accumulated Ten-year Radiation Dose in the Study Population.



The results of the test of the reliability of film badge use in the study population are shown in Table 1 (page 38). The opinions of the two supervisors are presented separately with respect to the same employees (for example, two employees were rated as "unreliable" by Supervisor No. 1, and as "probably reliable" by Supervisor No. 2). The results in Table 1 should not be taken very seriously, since the test was very subjective, but as they stand, they are encouraging. Out of 41 employees who were known to both supervisors, 34 (83%) were rated as at least "probably reliable" and only one (3%) as "unreliable" by both respondents.

Table 1. The Reliability of Film Badge Use in the Study Population. The Results of Querying Two Supervisors.

Number of individuals						
		Supervisor No. 1				
		(A)	(B)	(C)	(D)	Total
Supervisor No. 2	Unreliable (A)	1	2		1	4
	Probably reliable (B)	2	13		9	25
	Certainly reliable (C)	2	18	3	6	29
	Don't know (D)	3	13		31	47
	Total	9	46	3	47	105

The Medical Examination Results

The frequency distributions of the age at entry to the study and the year of entry to the study in the study population are included in Appendix D.

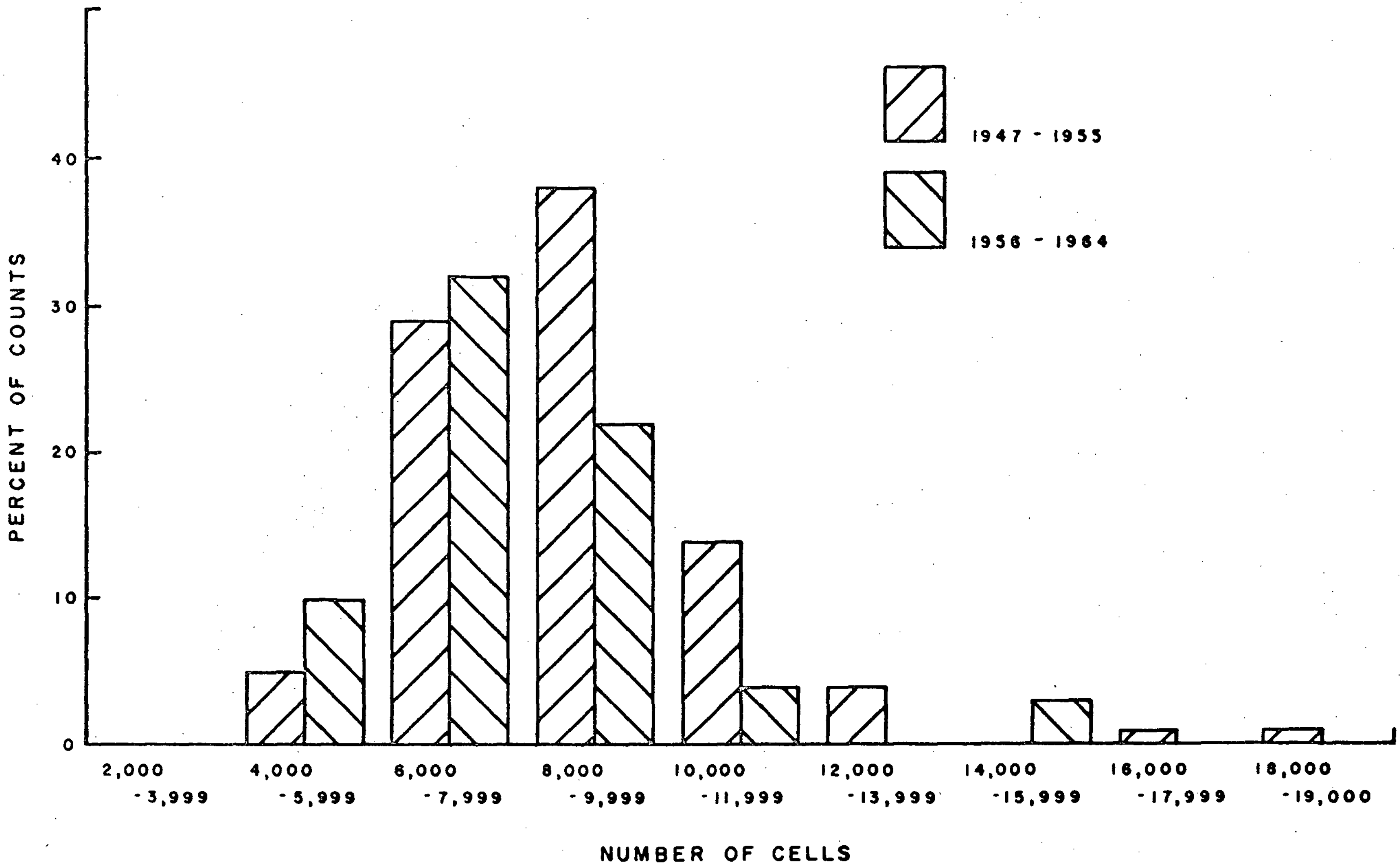
The differential leucocyte counts which were repeated in six blood smear slides from one study subject are shown in Table 2 (page 40). The slides were selected to represent counts made over the entire data collection period. The differential counting technique, as carried out at the Laboratory, seems to be reliable, since no consistent differences were found in recounting the slides.

Table 2. The Results of Repeating Some Differential Leucocyte Counts in Subject No. 57. Recounted March 26, 1967.

Date of original count		Percentage of total leucocytes					
		Neut.		Eos.	Bas.	Lym.	Mono.
		Fil.	Non-fil.				
7-20-48	(Original)	77		2	1	14	6
	(Recount)	80		2		10	8
8-30-48	(Original)	65		4		22	9
	(Recount)	66		1	1	24	8
6-13-49	(Original)	67	10	1		15	7
	(Recount)	79		1	1	17	3
8-13-61	(Original)	70		4	1	23	2
	(Recount)	70	1	1		22	6
5-28-62	(Original)	55		9	2	31	3
	(Recount)	54		8	3	31	4
9-3-63	(Original)	61		3	1	30	3
	(Recount)	67				28	5

In Figure 3 (page 42), a comparison was made of the reported leucocyte counts during the periods 1947-55 and 1956-64 in ten randomly selected members of the study population. The figure represents the frequency distributions of the counts during the two time periods. The means of the two distributions were 9,010 and 8,510 cells/mm^3 respectively, and the figure clearly shows that counts above 8,000 cells/mm^3 were more common in this group before 1956 than after it.

Figure 3. A Comparison of the Frequency Distributions of Leucocyte Counts During the Periods 1947-55 and 1956-64 in Ten Members of the Study Population.



In Figure 3 (page 42), a picture is presented of a general reduction of leucocyte counts from initial high values in the study population. The characteristics of the trend are further illustrated in Table 3 (page 44), a tabulation of the initial leucocyte count (on entering the study) and the subsequent trend of the leucocyte counts (measured as the coefficient of the regression of the count on time) in each of the 105 study subjects. Table 3 shows a trend toward expected values in individuals with relatively high and low initial counts, a tendency which was particularly marked in individuals with initial leucocyte counts of at least 10,000 cells/mm^3.

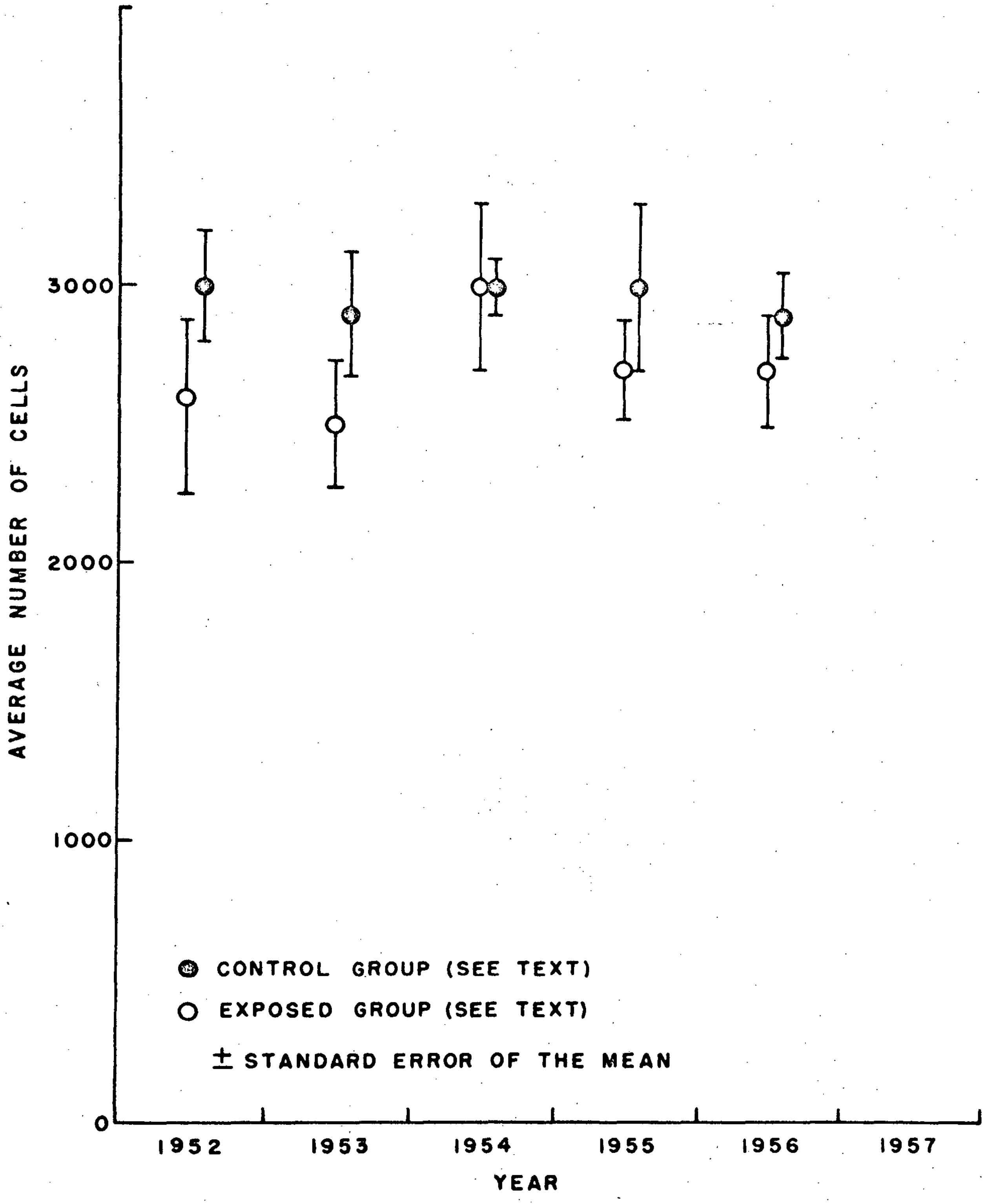
Table 3. The Two-way Frequency Distribution of the Leucocyte Count on Entrance to the Study and the Regression of the Leucocyte Count on Time in the Individuals in the Study Population.

Number of individuals						
Reg. coeff.	Number of cells (mm^{-3})					
	< 3999	4000 - 5999	6000 - 7999	8000 - 9999	>10000	Total
≥ 1.00		1				1
0.50 to 0.99		2	3	2		7
0.00 to 0.49		2	13	6	3	24
0.00 to -0.49		4	11	12	5	32
-0.50 to -0.99		1	6	11	12	30
≤-1.00			1	1	9	11
Total		10	34	32	29	105

In Figure 4 (page 46), lymphocyte count data from the present study at Berkeley are shown as a comparison with the results from the Los Alamos Scientific Laboratory (Figure 1, page 10). The data points in Figure 4 were produced by an averaging process like that used by Carter and Worman (1952), except that the unit time period was one year. The "exposed" group was made up of the ten individuals with the highest accumulated doses (33 to 87 rems) in the study population. The "control" group was composed of the ten individuals with the lowest doses (3 to 6 rems). In Figure 4, although the data points for the "exposed" group were below those for the "control" group in four cases out of five, the standard errors of the means were so large that no difference could be demonstrated between the two groups. In addition, the lymphocyte counts presented in Figure 4 were generally high compared to those seen in the Los Alamos data.

The investigations at Berkeley and Los Alamos were very different in the amounts of available hematological data. In the Berkeley study, there were some 20 to 30 hematological examinations made for each subject during his ten-year data collection period. Carter and Worman, on the other hand, were able to make use of 80 to 200 examinations for each subject over a 4.5 year period, a yearly examination frequency about ten times that at Berkeley.

Figure 4. The Trend of the Average Lymphocyte Counts Over Time in Workers at the Lawrence Radiation Laboratory, Berkeley, 1952-1956.



The Results of the Mathematical Analysis

The first part of the data analysis was a measurement in each subject of the partial correlation of medical examination results with the accumulated dose and with age at each examination date. The results of this test are shown in Table 4 (page 48). The entry in each column is the numerical average of all of the partial correlations for each examination procedure. The study population was divided into subgroups with relatively low and high doses and the analysis was repeated as a test of the validity of the results, i.e., any effect seen to be proportional to dose in the total population should be less prominent in the dose group below one rem per year and more obvious in the dose group above one rem per year.

In several cases, the average of the partial correlations was not equal to zero at the 0.05 level. This was particularly marked in the case of leucocytes and total neutrophils, both in the group as a whole (N = 105), and in the high-dose subgroup.

Table 4. The Average Partial Correlation of Medical Examination Results with the Accumulated Radiation Dose After the Effect of Age Is Removed.

Medical examination procedure	Average partial correlation (Marked * if the average is different from zero at the 0.05 level)		
	Dose < 1 rem per yr. (N = 51)	All doses (N =105)	Dose ≥ 1 rem per yr. (N = 54)
Weight	0.051	0.041	0.032
Urine specific gravity	-0.076	0.072 *	-0.068
Hemoglobin	0.159 *	0.104 *	0.052
Erythrocytes	-0.063	-0.050	-0.037
Leucocytes	0.029	0.058 *	0.085 *
Total neutrophils	0.029	0.055 *	0.080 *
Non-filamented neutrophils	-0.015	-0.005	0.004
Eosinophils	0.003	0.000	-0.002
Basophils	0.016	0.017	0.018
Lymphocytes	-0.050	0.006	0.060
Monocytes	0.124 *	0.064 *	0.005
Platelets	-0.004	-0.010	-0.015
Atypical erythrocytes	-0.027	-0.008	0.010 *
Atypical platelets	0.002	-0.016	-0.034 *
Atypical lymphocytes	-0.078 *	0.014	-0.006
Other atypical leucocytes	0.025	-0.005	-0.034 *

The second part of the data analysis was carried out in two steps. The first step was a computation for each medical procedure of the regression of the results on time in each of the 105 study subjects. The frequency distributions of the resulting regression coefficients are included in Appendix D. These data are summarized in Table 5 (page 50), which includes results in terms of the ten-year study period, in order to make the coefficients easier to visualize.

The time-regression coefficients of medical procedures which were coded and analyzed in terms of the original numerical values (weight, urine specific gravity, erythrocyte and leucocyte counts) produced frequency distributions which were approximately normal. The results of the other medical procedures were coded on a yes-or-no basis (see Appendix C) and their regression coefficients produced non-normal distributions with large excesses of zero values and wide scattering of positive and negative values around the mean.

The means of the frequency distributions were significantly ($p < 0.05$) different from zero in 13 cases, indicating that there was a general tendency of the results of these medical procedures to change with time. There were marked trends in the results of some of the procedures (see Table 5). Over the ten-year study period, the average increase in body weight was ten pounds, the average erythrocyte count decreased by about 0.3 million cells/mm^3, and

Table 5. The Trends in the Results of Medical Examinations Over a Ten-year Period. The Distribution of the Simple Linear Regression Coefficients.

Medical examination procedure		Regression coefficients				
		Per day		Per ten-year period		
Name	Units	Mean of reg. coefficients	Stand. error of mean	Mean of reg. coefficients	Stand. error of mean	Signif. level (1)
Weight	Pounds	2.60×10^{-3}	3.70×10^{-4}	9.50	1.35	< 0.01
Urine specific gravity	No units	-8.01×10^{-7}	1.70×10^{-7}	-0.00293	0.000620	< 0.01
Hemoglobin	Gm/100ml	5.20×10^{-7}	2.55×10^{-5}	0.00190	0.0930	< 0.99
Erythrocytes	$10^6/mm^3$	-8.34×10^{-5}	2.82×10^{-5}	-0.304	0.131	< 0.05
Total leucocytes	Mm^{-3}	-3.16×10^{-1}	5.43×10^{-2}	-1150.	198.	< 0.01
Total neutrophils	Mm^{-3}	-1.81×10^{-1}	4.26×10^{-2}	-662.	155.	< 0.01
Non-fil. neutrophils	Mm^{-3}	-2.93×10^{-2}	2.95×10^{-3}	-107.	10.7	< 0.01
Eosinophils	Mm^{-3}	-1.19×10^{-2}	5.87×10^{-3}	-43.5	21.5	< 0.05
Basophils	Mm^{-3}	-4.34×10^{-3}	1.71×10^{-3}	-15.8	6.23	< 0.02
Lymphocytes	Mm^{-3}	-4.31×10^{-2}	1.81×10^{-2}	-158.	56.3	< 0.01
Monocytes	Mm^{-3}	-7.13×10^{-2}	7.25×10^{-2}	-260.	25.9	< 0.01
Platelets	(2)	-1.53×10^{-6}	2.60×10^{-6}	-0.00559	0.00950	< 0.60
Atypical erythrocytes	(2)	1.23×10^{-6}	1.27×10^{-6}	0.00450	0.00463	< 0.40
Atypical platelets	(2)	1.45×10^{-5}	3.78×10^{-6}	0.0530	0.0138	< 0.01
Atypical lymphocytes	(2)	7.33×10^{-5}	6.80×10^{-6}	0.268	0.0248	< 0.01
Other atyp. leucocytes	(2)	4.51×10^{-6}	2.60×10^{-6}	0.0165	0.00263	< 0.01

1. Result of testing the probability that the "true" mean is not equal to zero by "Student t" test.
2. See coding instructions in Appendix C.

the average leucocyte count decreased by about 1,000 cells/ mm^3. The drop in leucocytes was apparently due to a decrease in all cell types. The results for the appearance of atypical blood cells are more difficult to interpret, since the time-regression coefficients for these medical procedures were not normally distributed, but there seems to have been increased reporting of these cell types as the study period progressed.

In some of the medical procedures, the extreme values of the time-regression coefficients were quite large, implying that there were marked changes in a few individuals over the ten-year period. For instance, 5% of them gained 33 pounds or more, and 10% of them reported a drop of 1.5 million cells/mm^3 or more in erythrocyte counts. Generally, the maximum and minimum values indicated for the ten-year changes in blood cell count results were on the order of one-fourth to one-half of the "normal" mean values for blood cell counts suggested by Wintrobe (1961). The results for the other medical procedures showed no such striking changes with time.

The next step in the data analysis was the entry of the time-regression coefficient for each medical procedure as the dependent variable in a multiple regression analysis. In this analysis, the independent variables were the radiation dose, age, and year of entry to the study.

For each medical procedure, two kinds of final results were produced, the multiple correlation coefficient and the multiple regression equation, each with its associated statistics.

As a preliminary to the calculation of the regression equations, the correlation coefficient (Pearson r) was calculated for all pairs of dependent and independent variables. The results are shown in Table 6 (page 53). When the trends in blood cell count results (erythrocytes, leucocytes, differential leucocytes) were compared with each other, the resulting correlations were generally significantly positive, indicating that these results tended to change with time in a similar manner throughout the study population. A significant negative correlation was found in the comparison of the radiation dose and the year of entry to the study, a reasonable outcome, considering the general trend to lower doses with time in the Laboratory.

Table 6. The Inter-correlations of the Experimental Variables.

Variable	Correlation with variable Marked (*) if significant at 0.05 level (two-tailed test)																	
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Weight	0.027	-0.002	-0.281 *	-0.092	-0.158	-0.105	-0.091	-0.049	0.098	-0.019	-0.001	0.087	-0.232 *	-0.072	-0.106	-0.105	-0.133	-0.006
2. Urine spec. grav.		0.100	0.082	-0.155	-0.215 *	0.065	-0.043	0.023	0.022	0.200 *	-0.116	-0.093	0.255 *	0.033	-0.001	-0.053	0.035	0.150
3. Hemoglobin			0.177	0.046	0.024	0.002	0.044	0.070	0.073	0.032	-0.106	0.076	-0.113	0.084	0.024	-0.029	0.050	0.039
4. Erythrocytes				0.238 *	0.179	-0.004	0.041	0.199 *	0.278 *	-0.091	-0.019	0.052	-0.052	0.252 *	0.065	0.308 *	0.076	0.070
5. Total leucocytes					0.937 *	0.255 *	0.397 *	0.300 *	0.535 *	0.285 *	-0.077	0.025	-0.067	-0.041	0.116	0.002	0.022	-0.011
6. Total neutrophils						0.217 *	0.325 *	0.197 *	0.297 *	0.196 *	-0.071	0.016	-0.040	-0.066	0.125	-0.027	0.048	0.009
7. Non-fil. neut.							0.292 *	0.049	0.088	0.244 *	0.009	0.033	-0.003	0.056	-0.052	0.087	-0.078	0.026
8. Eosinophils								0.238 *	-0.050	0.257 *	0.069	0.057	0.092	-0.005	0.093	-0.046	0.247 *	0.152
9. Basophils									0.158	0.163	0.227 *	0.013	-0.123	0.022	0.108	0.097	-0.027	-0.126
10. Lymphocytes										-0.018	-0.296 *	0.071	-0.131	0.026	-0.082	0.114	-0.184	-0.046
11. Monocytes											-0.203 *	-0.157	0.139	-0.018	0.200 *	-0.033	0.146	-0.037
12. Platelets												0.005	0.021	0.164	0.132	-0.156	-0.091	-0.076
13. Atyp. erythrocytes													0.006	-0.079	-0.084	0.038	0.044	-0.040
14. Atyp. platelets														0.085	0.168	0.024	0.110	0.112
15. Atyp. lymphocytes															0.048	-0.028	-0.068	-0.024
16. Other atyp. leuc.																0.010	0.158	0.029
17. Acc. radiation dose																	-0.075	-0.262 *
18. Age at entry																		0.038
19. Year of entry																		

1. Medical examination results expressed as the coefficient of the regression on time.

Table 7 (page 55) shows the results of the multiple regression analysis. The multiple correlation coefficients for urine specific gravity, monocyte counts, and atypical platelets were significant at the 0.05 level. The general failure of the independent variables to account for the sources of variation in the results was shown by the magnitude of the coefficients of multiple determination, which ranged up to a maximum of only 0.18 in the results for urine specific gravity, and were generally less than 0.01.

The regression coefficient which related the trend in medical examination results to the radiation dose was not significant at the 0.05 level in any case tested. The study hypothesis was not rejected in any medical procedure, i.e., any effects of occupational radiation exposure in this population were not of sufficient magnitude to be detectable in the multiple regression analysis.

The regression coefficient which compared the trend in medical examination results with the age at entry to the study was significant at the 0.01 level in the case of body weight. The coefficient was negative, indicating that the younger persons in the study gained weight faster than the older ones. There were no other significant results in this category.

Table 7. The Effects of Accumulated Radiation Dose, Age, and Year of Entry to the Study on Medical Examination Results.

Examination procedure	Multiple correlation			Multiple regression						
	Coeff. of multiple determ.	Multiple correl. coeff.	Signif. level	Constant	Radiation dose		Age at entry		Year of entry	
					Coefficient	Signif. level	Coefficient	Signif. level	Coefficient	Signif. level
Weight	0.046	0.214	< 0.10	1.46×10^{-2}	-8.38×10^{-6}	0.721	-1.31×10^{-4}	0.011	-1.52×10^{-4}	0.282
Urine specific gravity	0.177	0.421	< 0.001	-1.57×10^{-5}	8.20×10^{-9}	0.414	-1.31×10^{-8}	0.544	3.01×10^{-7}	< 0.001
Hemoglobin	0.043	0.207	< 0.10	-1.37×10^{-3}	5.73×10^{-7}	0.723	3.36×10^{-6}	0.338	2.48×10^{-5}	0.012
Erythrocytes	0.008	0.092	< 0.50	-8.98×10^{-4}	-2.08×10^{-6}	0.319	2.93×10^{-6}	0.516	1.50×10^{-5}	0.234
Total leucocytes	< 0.001	< 0.001	< 0.75	1.02×10^{0}	-2.89×10^{-3}	0.415	4.20×10^{-3}	0.584	-2.82×10^{-2}	0.188
Total neutrophils	< 0.001	< 0.001	< 0.50	8.42×10^{-1}	-1.56×10^{-3}	0.574	5.24×10^{-3}	0.384	-2.31×10^{-2}	0.169
Non-filamented neutrophils	< 0.001	< 0.001	< 0.90	-9.33×10^{-2}	7.58×10^{-5}	0.695	2.02×10^{-4}	0.630	1.11×10^{-3}	0.340
Eosinophils	< 0.001	< 0.001	< 0.90	-9.42×10^{-2}	-1.08×10^{-4}	0.779	-3.89×10^{-5}	0.963	1.69×10^{-3}	0.468
Basophils	< 0.001	< 0.001	< 0.90	-1.68×10^{-2}	3.40×10^{-5}	0.762	-1.38×10^{-4}	0.571	3.24×10^{-4}	0.632
Lymphocytes	< 0.001	< 0.001	< 0.75	4.20×10^{-1}	-1.13×10^{-3}	0.340	2.62×10^{-4}	0.918	-8.98×10^{-3}	0.208
Monocytes	0.049	0.222	< 0.05	-4.09×10^{-1}	2.93×10^{-4}	0.515	-1.06×10^{-3}	0.274	7.27×10^{-3}	0.008
Platelets	< 0.001	< 0.001	< 0.90	3.96×10^{-5}	1.64×10^{-9}	0.992	-2.82×10^{-7}	0.446	-6.36×10^{-7}	0.538
Atypical erythrocytes	< 0.001	< 0.001	< 0.99	9.06×10^{-7}	-2.56×10^{-8}	0.759	-3.98×10^{-8}	0.825	4.01×10^{-8}	0.936
Atypical platelets	0.073	0.270	< 0.025	-2.30×10^{-4}	1.16×10^{-7}	0.624	2.64×10^{-7}	0.606	4.64×10^{-6}	0.001
Atypical lymphocytes	0.011	0.105	< 0.25	-9.02×10^{-5}	-2.28×10^{-7}	0.604	-1.05×10^{-6}	0.272	3.98×10^{-6}	0.136
Other atypical leucocytes	0.001	0.027	< 0.50	-7.89×10^{-5}	-3.56×10^{-8}	0.832	5.74×10^{-8}	0.875	1.63×10^{-6}	0.110

1. Medical examination results expressed as the coefficient of the regression on time.

The regression coefficient which related the trend in medical examination results with the year of entry to the study was significant at the 0.05 level in several medical procedures, including urine specific gravity, hemoglobin concentration, monocyte count, and atypical platelet count. Three of these procedures also produced multiple correlation coefficients which were significant at the 0.05 level.

DISCUSSION

The Trends in the Results of Medical Examinations

The partial correlation analysis yielded no results which could positively be identified as effects of radiation exposure. Although a number of the averages of the correlation coefficients were significantly different from zero, the results did not form a pattern consistent with other findings in mammalian radiobiology. Leucocyte and neutrophil counts, for instance, were positively associated with increasing dose, an unlikely outcome from exposure to an agent which is expected to depress blood cell counts. The lymphocyte count is generally regarded as a sensitive index of radiation exposure, but in this case no significant associations were found with dose. Radiation dose and age both accumulate in a manner which is highly dependent on the passage of time. The strong associations found in the partial correlation analysis were probably a reflection of the marked trends over time in the data (see Table 5, page 50).

In the regression analysis which followed, the comparison of medical examination results with doses could be made without any consideration of elapsed time. The regression analysis of each medical procedure began with a determination of the regression on time of the results of that procedure in each of the 105 study subjects. The frequency distributions were examined in order to describe the trends of the original data. Particular attention was paid to the leucocyte count, which was considered to be important as a possible indicator of radiation exposure and because it was used as a multiplying factor in calculating the absolute values of the differential leucocyte counts.

The means of the regression coefficients were significantly less than zero in the cases of the erythrocyte, leucocyte, and differential leucocyte counts (see Table 5, page 50). Over the ten year study period, the indicated average decreases in erythrocyte and leucocyte counts were 304,000 and 1,150 cells/mm^3 respectively. Radiation dose and age both accumulate with time, so this finding was in agreement with the results of the partial correlation analysis in the original analysis scheme.

Some thought was given to possible reasons for the seeming decline in blood cell counts over time in this group of employees.

The decline in blood cell counts could not have been due to pure chance, considering the amount of data, the number of subjects, and the agreement in the results.

Changes in blood cell counting techniques were not likely to have had any major effect on the results of these procedures. Substantially the same group of laboratory technicians has been performing the hematology procedures since the late 1940's. The blood cell counting methods have not changed since 1944, except for the erythrocyte count, which was no longer included in the routine hematology procedures after the technique was changed in 1959 (see Appendix B). In the multiple regression test, no significant influence was found of the year of entrance to the study on the rate of change of the erythrocyte and leucocyte counts, such as might be expected as a result of a change in technique.

The employees in the study population were all chosen because of recorded radiation exposures in varying amounts. Possibly, the irradiation itself may have been responsible for some of the decline in blood cell counts, since this is the effect that was expected, but that it had more than a minor effect on the results is unlikely for several reasons. The overall trend in leucocyte count results was a progression from values which were higher than expected down to values within the expected range. The results in Figure 3 (page 42) show a much higher proportion of leucocyte counts over 10,000 cells/mm^3 before 1956 than after. In the multiple regression analysis, the argument was that, since radiation exposure has a depressant effect on blood cell counts, the employees with relatively high radiation doses should show a more marked downward trend in blood cell counts than those with low doses. The radiation effect should be superimposed on any other general trends over time in the medical data. The results of the multiple regression analysis showed no such effect of radiation exposure on the trends in blood cell counts.

Each person in the group experienced ten years of aging during his data collection period. According to Wintrobe (1961), no evidence is available for an effect of aging on blood cell counts in normal males during the period from 25 to 50 years of age. No significant associations were found between trends in blood cell counts and age at entry to the study in the multiple regression analysis. (This finding does not rule out the possibility of a constant rate of decrease in blood cell counts with advancing age). Aging cannot likely account for more than a minor part of the marked trends that were found in the reported blood cell counts.

The study population seems to have had a general mild erythrocytosis and a more marked leucocytosis during the early part of the 1947-1965 data collection period. As the data collection progressed, the blood cell counts decreased to values within the expected range. This conclusion is supported by the data in Figure 3 (page 42), which shows an excess of leucocyte counts over 10,000 cells/mm^3 during the years from 1947 to 1955. It is further supported by the finding reported in Table 3 (page 44), that the individuals in the study population with relatively high initial leucocyte counts had a greater than average tendency to a subsequent depression.

Wintrobe (1961) notes that physical and emotional stresses may result in erythrocytosis and leucocytosis. The period from 1947 to 1955 was an extremely busy one for many of the technical and craft employees at the Laboratory, since both of the large accelerators and several smaller ones were built or completely rebuilt during this time. Persons associated with the accelerators frequently worked long and irregular hours and it is possible that exposure to these working conditions may have contributed to the observed high blood cell counts. This is an interesting possibility which will have to remain conjectural, since there is a lack of available data on actual working conditions with which to test it.

The existence of trends over time in the blood count data complicated any comparison with other variables over time.

The Effects of Radiation Dose on the Results of Medical Examinations

The study hypothesis, that there are no physiological effects of occupational radiation exposure, was tested by an indirect method. A measurement was made of the effect of an accumulated radiation dose on the trends in the results of routine medical examination procedures. The study hypothesis was not rejected for any medical procedure tested, so there were no physiological effects of occupational radiation exposure shown in this study. This conclusion did not agree with the results of the similar inquiry at the Los Alamos Scientific Laboratory by Carter and Worman (1952).

In the present investigation at Berkeley, out of a study population of 105 employees, there were 8 who had accumulated ten-year doses of 48 to 87 rems and 97 who had doses ranging from 3 to 44 rems. Assuming that the dose units were equivalent, there was a similar number and proportion of persons with significant radiation doses in both study populations.

In the present study, an average downward trend was found in lymphocyte counts in the entire study population (see Table 5, page 50). The average of the regression coefficients was -158 cells per mm^3 per ten-year period, which was significant at the 0.01 level. In the eight individuals with doses of 48 to 87 rems, the average ten-year diminution in lymphocyte counts was -610 cells, which at first glance is comparable with the results presented by Carter and Worman (see page 11). However, inspection of the distribution of the time-regression coefficients for lymphocyte counts (see Appendix D) revealed that about 25% of them were less than -0.174 cells per day, a value which is equivalent to -610 cells in ten years, so that the above apparent correspondence in results was fortuitous.

A comparison of the lymphocyte counts from the study at Los Alamos in Figure 1 (page 10) with those from the present study at Berkeley in Figure 4 (page 46) shows that the standard errors of the means in the "exposed" groups were much larger in the Berkeley data. This difference in standard errors was probably largely a consequence of the relative amounts of hematological data used to establish the data points in Figures 1 and 4. As was mentioned above (page 45), the examination frequency at Los Alamos was about ten times that at Berkeley. One can reasonably conclude that the results of the study at Berkeley might very likely have agreed with those from Los Alamos if there had been similar amounts of data available in the two studies.

The apparent lack of any physiological effects of radiation in the results of this study is an argument in favor of the present standards for occupational radiation exposure, particularly when one considers that some members of the study population were exposed at rates which were almost double the standard, over a period of ten years.

This investigation utilized medical examination results collected over a total period of 18 years, a long time for a retrospective epidemiological study. The demonstration of prominent and not readily explainable trends over time in these data is worth the attention of other investigators planning studies of this general type.

CONCLUSIONS

1. No physiological effects of routine occupational radiation exposure were found in the results of routine hematological examinations in 105 workers at the Lawrence Radiation Laboratory, Berkeley.

2. There were prominent, long-term trends in the medical examination results which confused the mathematical analysis, and which could not be explained by the use of available data.

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APPENDICES

Appendix A. The Medical Examination Forms.

University of California
Lawrence Radiation Laboratory
Medical Dept.

HEMATOLOGY

Date	Name
	Hemoglobin
	Hematocrit (Micro)
	White Blood Cell Count
	Segmented Neutrophiles
	Band Neutrophiles
	Eosinophiles
	Basophiles
	Lymphocytes
	Monocytes
	Platelets
	RBC Morphology
	Sickle Prep.

RL-777-2 TECH:

University of California
Lawrence Radiation Laboratory
Medical Dept.

URINALYSIS

Date	Name
	Appearance
	Color
1.0	Specific Gravity
A	Reaction
	Protein
	Sugar
	Acetone
	White Blood Cells/HPF
	Red Blood Cells/HPF
	Casts
	Crystals

RL-778-2 TECH:

PHYSICAL EXAMINATION RECORD	UNIVERSITY OF CALIFORNIA LAWRENCE RADIATION LABORATORY	Type of Exam.	Pre-placement		Special		Re-employment	
			Periodic		Termination			

Last name	First name	Middle Initial	Home address	
			Telephone number	Date of Exam.

Date of birth	Race	Sex M F	Marital status S M W D	Name of spouse	Number of children

Title	Type of work	Department and Supervisor	Places of work

FAMILY HISTORY

Please answer the following questions, or fill in the blanks to the best of your ability.

Father: Living ☐ Well ☐ Sick ☐ Dead ☐ Cause of death.................................

Mother: Living ☐ Well ☐ Sick ☐ Dead ☐ Cause of death.................................

No. of brothers Living ☐ Dead ☐ Cause of death.................................

No. of sisters Living ☐ Dead ☐ Cause of death.................................

Has any relative ever been ill with

Cancer..................	Yes ☐	No ☐	Relation?..................................
Nervousness......	Yes ☐	No ☐	Relation?..................................
Diabetes............	Yes ☐	No ☐	Relation?..................................
Heart trouble	Yes ☐	No ☐	Relation?..................................
Epilepsy..............	Yes ☐	No ☐	Relation?..................................
Stroke..................	Yes ☐	No ☐	Relation?..................................
Asthma................	Yes ☐	No ☐	Relation?..................................
Tuberculosis........	Yes ☐	No ☐	Relation?..................................

PERSONAL HISTORY

		Details (Include dates)
Have you ever been postponed, rated up, or rejected for insurance, received benefits or compensation, or been rejected for employment or by the Army or Navy because of a physical condition?	Yes ☐ No ☐	
Are you now in sound health and without physical or mental defects or infirmities of any kind?	Yes ☐ No ☐	
Have you ever had a surgical operation, either major or minor?	Yes ☐ No ☐	
Have you ever received treatment at a Hospital, Sanatorium or Clinic?	Yes ☐ No ☐	
Name any serious illnesses, give name and address of attending physicians.	Yes ☐ No ☐	
Have you ever had any serious accidents or injuries?	Yes ☐ No ☐	
Have you ever had a hernia or worn a truss?	Yes ☐ No ☐	
Has your weight changed in the last year? Gained or lost? How much?	Yes ☐ No ☐	
Have you ever had X-ray or radium treatment of any kind?	Yes ☐ No ☐	
Have you ever had any disease of the blood or bleeding tendencies?	Yes ☐ No ☐	
Have you ever had to change residence or occupation for health reasons?	Yes ☐ No ☐	

Are you now bothered with, or have you ever had severe complaints of:

Allergies....................	Yes ☐	No ☐	Ages..................yrs.
Anemia......................	Yes ☐	No ☐	Ages..................yrs.
Appendicitis..............	Yes ☐	No ☐	Ages..................yrs.
Asthma......................	Yes ☐	No ☐	Ages..................yrs.
Backache....................	Yes ☐	No ☐	Ages..................yrs.
Bladder trouble..........	Yes ☐	No ☐	Ages..................yrs.
Blood disease............	Yes ☐	No ☐	Ages..................yrs.
Blood spitting............	Yes ☐	No ☐	Ages..................yrs.
Broken bones............	Yes ☐	No ☐	Ages..................yrs.
Chest pain..................	Yes ☐	No ☐	Ages..................yrs.
Constipation..............	Yes ☐	No ☐	Ages..................yrs.
Convulsions..............	Yes ☐	No ☐	Ages..................yrs.
Diabetes....................	Yes ☐	No ☐	Ages..................yrs.
Diarrhea....................	Yes ☐	No ☐	Ages..................yrs.

[OVER]

Dizziness	Yes ☐ No ☐	Ages	yrs.
Ear trouble	Yes ☐ No ☐	Ages	yrs.
Epilepsy	Yes ☐ No ☐	Ages	yrs.
Eye trouble	Yes ☐ No ☐	Ages	yrs.
Fainting	Yes ☐ No ☐	Ages	yrs.
Frequent headache	Yes ☐ No ☐	Ages	yrs.
Hay Fever	Yes ☐ No ☐	Ages	yrs.
Heart trouble	Yes ☐ No ☐	Ages	yrs.
High blood pressure	Yes ☐ No ☐	Ages	yrs.
Insomnia	Yes ☐ No ☐	Ages	yrs.
Jaundice	Yes ☐ No ☐	Ages	yrs.
Kidney trouble	Yes ☐ No ☐	Ages	yrs.
Malaria	Yes ☐ No ☐	Ages	yrs.
Menstrual disorder	Yes ☐ No ☐	Ages	yrs.
Mononucleosis	Yes ☐ No ☐	Ages	yrs.
Nervous breakdown	Yes ☐ No ☐	Ages	yrs.
Nervousness	Yes ☐ No ☐	Ages	yrs.
Paralysis	Yes ☐ No ☐	Ages	yrs.
Persistent cough	Yes ☐ No ☐	Ages	yrs.
Persistent hoarseness	Yes ☐ No ☐	Ages	yrs.
Persistent low energy	Yes ☐ No ☐	Ages	yrs.
Pleurisy	Yes ☐ No ☐	Ages	yrs.
Pneumonia	Yes ☐ No ☐	Ages	yrs.
Poor appetite	Yes ☐ No ☐	Ages	yrs.
Rheumatic fever	Yes ☐ No ☐	Ages	yrs.
Rheumatism	Yes ☐ No ☐	Ages	yrs.
Scarlet fever	Yes ☐ No ☐	Ages	yrs.
Shortness of breath	Yes ☐ No ☐	Ages	yrs.
Sinusitis	Yes ☐ No ☐	Ages	yrs
Skin diseases	Yes ☐ No ☐	Ages	yrs.
Stomach ulcer	Yes ☐ No ☐	Ages	yrs.
Swelling of the feet	Yes ☐ No ☐	Ages	yrs.
Swollen lymph glands	Yes ☐ No ☐	Ages	yrs.
Syphilis	Yes ☐ No ☐	Ages	yrs.
Thyroid disturbances	Yes ☐ No ☐	Ages	yrs.
Tonsilitis	Yes ☐ No ☐	Ages	yrs.
Tuberculosis	Yes ☐ No ☐	Ages	yrs.
Tumors (benign or malignant)	Yes ☐ No ☐	Ages	yrs.
Vomiting of blood or black material	Yes ☐ No ☐	Ages	yrs.
Other diseases or conditions (explain below in detail)	Yes ☐ No ☐	Ages	yrs

EMPLOYMENT HISTORY

Name those positions you have held in which there was possible exposure to any poisons, chemicals, dusts, or radiation.

Name of concern	Location	Type of work	Name hazardous agents	Period of employment

FEMALES

Do you menstruate regularly? Yes☐ No☐ Any bleeding between periods? Yes☐ No☐ Details..........

Do you have to go to bed sometimes because of your periods? Yes ☐ No ☐

Date of last menstrual period: Month.......... from date.......... to date.......... year..........

Do you believe you are pregnant? Yes ☐ No ☐

REMARKS

Use this space for details and any conditions not covered above

....

....

....

....

I HEREBY DECLARE THAT MY ANSWERS TO THE PRECEDING MEDICAL QUESTIONNAIRE ARE COMPLETE AND TRUE. Date..........

Applicant's signature..........

DOCTOR'S REMARKS

History of melena?..........

....

....

GENERAL APPEARANCE

	Yes	No
Nutrition abnormal	☐	☐
Posture abnormal	☐	☐
Asthenic	☐	☐
Athletic	☐	☐
Obese	☐	☐
Pyknic	☐	☐
Abnormal body configuration	☐	☐

Temp.	Height	Weight
	in.	lbs.

FACE AND SKIN

	Yes	No
Plethora	☐	☐
Pallor	☐	☐
Pigmentation abnormal	☐	☐
Skin disease	☐	☐
Skin texture abnormal	☐	☐
Jaundice	☐	☐
Cyanosis	☐	☐
Hair texture abnormal	☐	☐
Hair dist. abnormal	☐	☐
Petechiae or ecchymosis	☐	☐
Scars		
Location		

LYMPH NODES

	Yes	No
Cervical adenopathy	☐	☐
Submental adenopathy	☐	☐
Epitrochlear adenopathy	☐	☐
Axillary adenopathy	☐	☐
Inguinal	☐	☐

EYES

	(R) Yes	(R) No	(L) Yes	(L) No
Corneae				
Abnormal	☐	☐	☐	☐
Conjunctivae				
Abnormal	☐	☐	☐	☐
Injected	☐	☐	☐	☐
Jaundiced	☐	☐	☐	☐
Sclerae abnormal	☐	☐	☐	☐
Pupils				
Irregular	☐	☐	☐	☐
Unequal	☐	☐	☐	☐
Abnormal Reaction to L	☐	☐	☐	☐
Abnormal Reaction to A	☐	☐	☐	☐
Acuity uncorrected	20/		20/	
Acuity corrected	20/		20/	

	yes	no
Abnormal color vision	☐	☐

EYES—(Continued)

	(R) Yes	(R) No	(L) Yes	(L) No
Retinae				
Hemorrhage of	☐	☐	☐	☐
Exudate of	☐	☐	☐	☐
Sclerosis of	☐	☐	☐	☐
Edema of discs	☐	☐	☐	☐
EOM abnormal	☐	☐	☐	☐
Xanthelasma	☐	☐	☐	☐
Arcus senilis	☐	☐	☐	☐
Edema of lids	☐	☐	☐	☐
Cataract	☐	☐	☐	☐
Exophthalmos	☐	☐	☐	☐
Strabismus	☐	☐	☐	☐
Ptosis	☐	☐	☐	☐
Nystagmus	☐	☐	☐	☐
Fields abnormal	☐	☐	☐	☐

EARS

	(R) Yes	(R) No	(L) Yes	(L) No
Cerumen	☐	☐	☐	☐
Purulent discharge	☐	☐	☐	☐
Perforation of M. T.	☐	☐	☐	☐
Abnormal aud. canal	☐	☐	☐	☐
Auditory acuity (Whispered voice)	/15		/15	
Mastoid tenderness	☐	☐	☐	☐

NOSE

	(R) Yes	(R) No	(L) Yes	(L) No
Septal deviation	☐	☐	☐	☐
Septal perforation	☐	☐	☐	☐
Mucosa pale	☐	☐	☐	☐
Mucosa congested	☐	☐	☐	☐
Anosmia	☐	☐	☐	☐
Enlarged turbinates	☐	☐	☐	☐
Tumors	☐	☐	☐	☐
Discharge	☐	☐	☐	☐

MOUTH

	Yes	No
Complete dentures	☐	☐
Partial dentures	☐	☐
Caries	☐	☐
Infection of gums	☐	☐
Retraction of gums	☐	☐
Metal line	☐	☐
Tongue		
Abnormal	☐	☐
Color abnormal	☐	☐
Lesions of	☐	☐
Papillary atrophy	☐	☐
	RL	
Deviation to	☐☐	☐

THROAT

	Yes	No
Pharynx		
Granular	☐	☐
Injected	☐	☐
Tonsils		
Absent	☐	☐
Small	☐	☐
Hypertrophic	☐	☐
Infected	☐	☐
Soft palate abnormal	☐	☐
Voice abnormal	☐	☐

NECK

	Yes	No
Thyroid		
Enlarged	☐	☐
Nodular	☐	☐
Abnormal pulsations	☐	☐

THORAX

	Yes	No
Asymmetrical	☐	☐
Flat	☐	☐
Emphysematous	☐	☐
Abnormal movement	☐	☐
Breasts		
Masses	☐	☐
Scars	☐	☐
Discharge	☐	☐
Tenderness	☐	☐
Nipples abnormal	☐	☐
Size abnormal	☐	☐
Lungs		
Resonance abnormal	☐	☐
Fremitus abnormal	☐	☐
Breath sounds abnormal	☐	☐
Rales	☐	☐

BACK

	Yes	No
Tenderness of spine	☐	☐
Limitation of movements	☐	☐
CVA tenderness	☐	☐
Scoliosis	☐	☐
Kyphosis	☐	☐
Lordosis	☐	☐

[OVER]

CARDIO-VASCULAR SYSTEM

Heart
Pulse rate ....
Blood pressure ....

	Yes	No
Heart enlarged to examination	☐	☐
Heart sounds abnormal	☐	☐
Heart sounds forceful	☐	☐
Heart sounds distant	☐	☐
Heart sounds reduplicated	☐	☐
Premature beats	☐	☐
Fibrillation	☐	☐
Thrills	☐	☐
Arrhythmia	☐	☐
Murmur	☐	☐

Describe

ABDOMEN

	Yes	No
Hepatic enlargement	☐	☐
Splenic enlargement	☐	☐
Renal enlargement	☐	☐
Masses	☐	☐
Herniae (abdominal)	☐	☐
Tenderness	☐	☐

INGUINAL REGION

	(R) Yes	(R) No	(L) Yes	(L) No
Relaxed rings	☐	☐	☐	☐
Hernia	☐	☐	☐	☐
Evidence of hernioplasty	☐	☐	☐	☐
Tussal impulse	☐	☐	☐	☐
Varicocele	☐	☐	☐	☐
Hydrocele	☐	☐	☐	☐
Femoral hernia	☐	☐	☐	☐

PERIPHERAL VESSELS

	Yes	No
Arteries		
Abnormal	☐	☐
Sclerotic	☐	☐
Tortuous	☐	☐
Varicosities	☐	☐

HANDS

Note abnormalities of finger tips, skin, etc.

EXTREMITIES

Note abnormalities, edema, etc.

SKELETAL SYSTEM

	(R) Yes	(R) No	(L) Yes	(L) No
Missing members	☐	☐	☐	☐
Upper extremities				
Deformities	☐	☐	☐	☐
Limitation of motion	☐	☐	☐	☐
Lower extremities				
Deformities	☐	☐	☐	☐
Limitation of motion	☐	☐	☐	☐

	Yes	No
Sternal or other bone tenderness	☐	☐

NEUROLOGICAL EXAM

	(R) Yes	(R) No	(L) Yes	(L) No
Reflexes, abnormal				
Biceps	☐	☐	☐	☐
Triceps	☐	☐	☐	☐
Abdominal	☐	☐	☐	☐
Cremasteric	☐	☐	☐	☐
Patellar	☐	☐	☐	☐
Achilles	☐	☐	☐	☐
Tremors	☐	☐	☐	☐
Gait impairment	☐	☐	☐	☐
Paralyses	☐	☐	☐	☐

Babinski ....
Romberg ....
Clonus ....
Evidence of emotional instability or personality deviation .... Yes ☐ No ☐
Slight ☐
Moderate ☐
Marked ☐

GENITALIA

	Yes	No
Male		
Penis abnormal	☐	☐
Testes abnormal	☐	☐
Masses	☐	☐
Cryptorchidism	☐	☐

Female
Bimanual pelvic .... done .... ☐
or
Bimanual rectal .... done .... ☐

	Yes	No
Vagina abnormal	☐	☐
Cervix abnormal	☐	☐
Fundus abnormal	☐	☐
Adnexa abnormal	☐	☐

RECTUM

	Yes	No
Hemorrhoids		
Internal	☐	☐
External	☐	☐
Prostate		
Hypertrophy	☐	☐
Abnormal consistency	☐	☐
Abnormal shape	☐	☐
Sphincter tone abnormal	☐	☐

POSITIVE FINDINGS—SUMMARY

ACCEPTED

REJECTED

RESTRICTIONS

Patient has been informed and advised regarding the above conditions.

SIGNATURE

M.D.

Appendix B. The Medical Examination Procedures.
Techniques.

Procedure	Technique	Reported as
Weight	Subjects are weighed clothed, except for shoes.	Pounds, to the nearest 1/4 pound.
Urine sp.g.	Hydrometer	Specific gravity, to the nearest 0.001.
Hemoglobin conc.	Cyan-methemoglobin method (Wintrobe, 1961).	Grams/100 ml., to the nearest 0.01 gram.
Erythrocyte count	Before 1959 - Enumerated in counting chamber. 1959 and after - Enumerated in flow counter ("Coulter counter").	Millions of cells per cubic mm., to the nearest 0.01 million.
Leucocyte count	Enumerated in counting chamber	Cells/cubic mm., to the nearest hundred.
Differential leucocyte count	Enumerated in dried blood smear. At least 100 cells counted.	Each cell type reported as per cent of total leucocytes, to the nearest 1 p.c.
Platelets	Before 1959 - Enumerated in counting chamber 1959 and after - Count estimated in blood smear.	Platelets/cubic mm. Less than, within, or greater than normal limits.
Atypical blood cells	Noted during enumeration of blood cells in counting chamber or in blood smear.	Reported as present, if seen.

Appendix C. The Medical Examination Procedures.
Coding Guide for Data Processing.

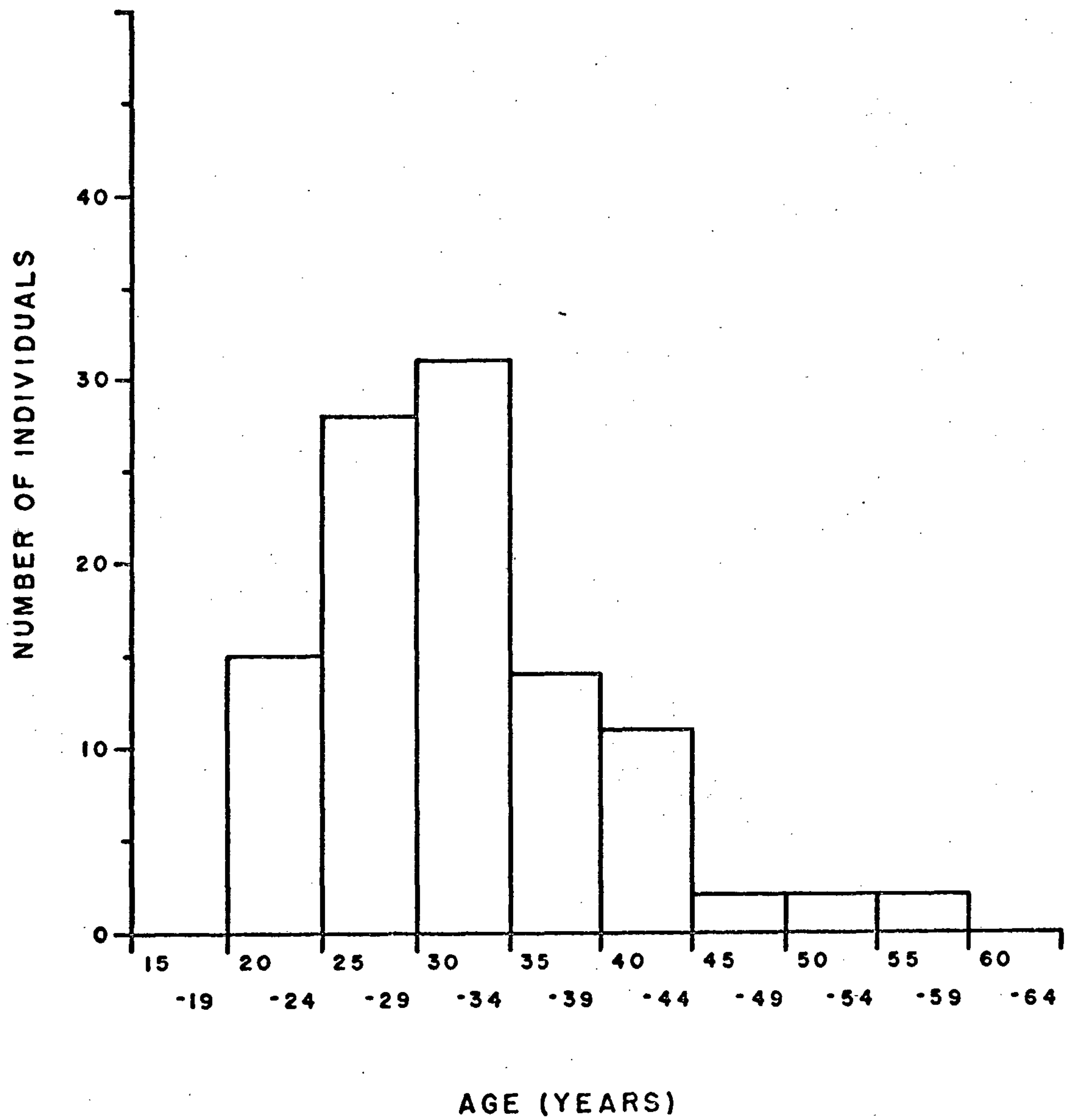
Card columns	Variable	Instructions
1	Type of card	Medical exam. results - code 1.
2- 4	Subject no.	
5-10	Date of exam.	Code month, day, last two digits of year.
11-13	Weight	Code weight in pounds, to the nearest whole pound.
14-16	Urine sp.g.	Code the 3 digits to the right of the decimal point.
17-19	Hemoglobin conc.	Code gm./100 ml., to the nearest 0.01 gm. Omit the decimal point.
20-22	Erythrocyte count	Code millions/cubic mm., to the nearest 0.01 million. Omit the decimal point.
23-25	Leucocyte count	Code hundreds/cubic mm., to the nearest hundred.
26-27	Neutrophil count	Code per cent, to the nearest 1 per cent.
28-29	Non-fil. neut. count	Code per cent, to the nearest 1 per cent.
30-31	Eosinophil count	Code per cent, to the nearest 1 per cent.
32-33	Basophil count	Code per cent, to the nearest 1 per cent.
34-35	Lymphocyte count	Code per cent, to the nearest 1 per cent.
36-37	Monocyte count	Code per cent, to the nearest 1 per cent.

Card columns	Variable	Instructions	
38	Platelet count	Count	Code
		< 150,000/cubic mm.	0
		150,000 to 500,000	1
		> 500,000/cubic mm.	2
39	Atypical erythrocytes	Not reported - code 0. Reported - code 1.	
40	Atypical platelets	Not reported - code 0. Reported - code 1.	
41	Atypical lymphocytes	Not reported - code 0. Reported - code 1.	
42	Other atyp. leucocytes	Not reported - code 0. Reported - code 1.	

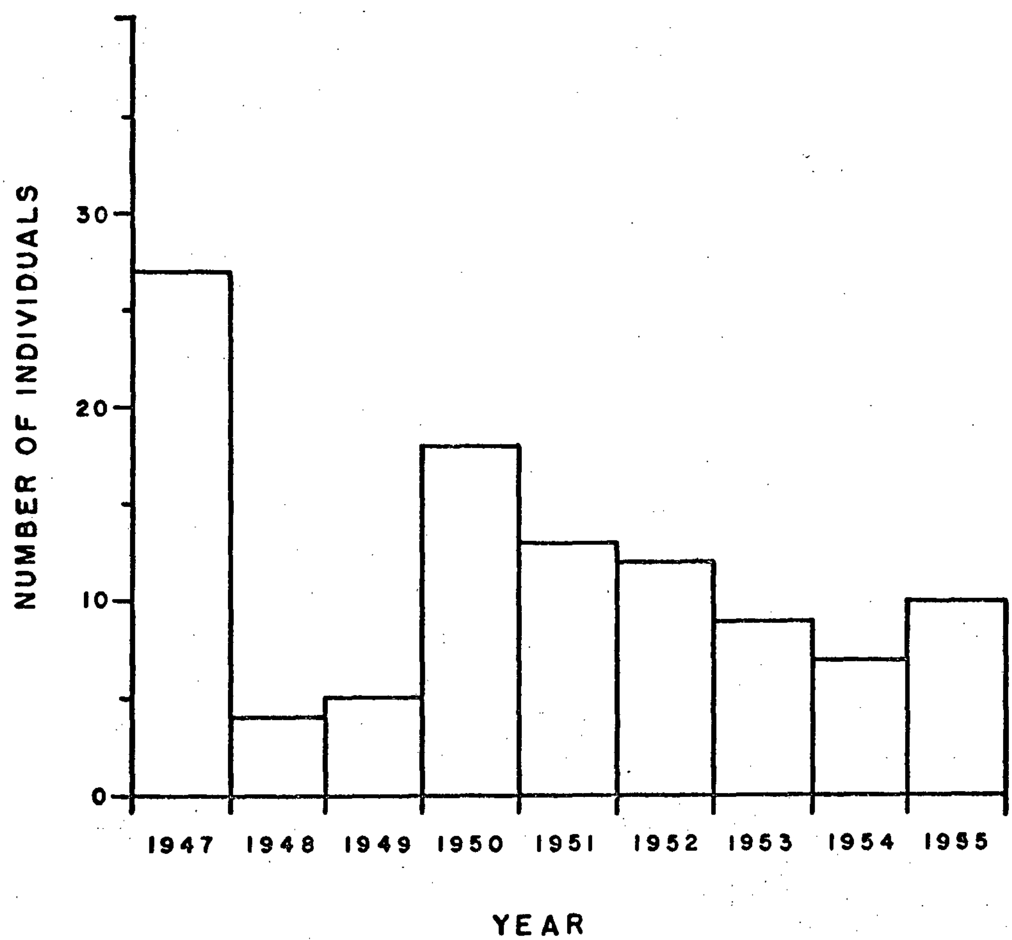
Note - if a datum is missing (as in examination not done), enter 9 in all columns of the corresponding field on the card.

Appendix D. The Frequency Distributions of the Variables (Except Dose) Entered in the Multiple Regression Program.

The Age at Entry to the Study.



The Year of Entry to the Study.



The Average Daily Change in Body Weight.

```
    MEAN =  2.598E-03,  STD. DEVIATION =  3.785E-03,  N =   105

       20++
          +
          +
          +
          +                                               111
       15++                                               111
          +                                               111
 C        +                                     111       111
 O        +                                     111       111  111
 U        +                                     111       111  111
 N     10++                                     111       111  111
 T        +                                     111  111  111  111  111
          +                                111  111  111  111  111  111
          +                                111  111  111  111  111  111  111
          +                                111  111  111  111  111  111  111
        5++                      111       111  111  111  111  111  111  111  111
          +                      111       111  111  111  111  111  111  111  111  111
          +                 111  111  111  111  111  111  111  111  111  111  111  111  111
          +       111       111  111  111  111  111  111  111  111  111  111  111  111  111  111  111
          +       111       111  111  111  111  111  111  111  111  111  111  111  111  111  111  111
        0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-     +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +
 TILES      0    0    2    2    5    10   13   20   33   41   57   68   77   83   88   92   95   97   99   99   99
            +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +
         -0.700    -0.500    -0.300    -0.100     0.100     0.300     0.500     0.700     0.900     1.100     1.300
              -0.600    -0.400    -0.200    -0.000     0.200     0.400     0.600     0.800     1.000     1.200

                 INTERVAL ENDPOINTS (UNITS OF 1.0E -2)


OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE      2
                  OBS. NUMBER     75, NAME '        ', IS  0.01521.
                  OBS. NUMBER     96, NAME '        ', IS -0.009686.
```

The Average Daily Change in Urine Specific Gravity.

```
MEAN = -8.012E-07,  STD. DEVIATION =  1.740E-06,  N =   105

      15++                                             111
         +                                             111
         +                         111                 111
         +                         111         111     111
         +                         111         111     111
C     10++                         111     111 111 111 111
O        +                         111 111 111 111 111 111
U        +                         111 111 111 111 111 111
N        +                     111 111 111 111 111 111 111
T        +                 111 111 111 111 111 111 111 111
       5++                 111 111 111 111 111 111 111 111     111
         +                 111 111 111 111 111 111 111 111     111
         +             111 111 111 111 111 111 111 111 111 111 111     111     111
         +         111 111 111 111 111 111 111 111 111 111 111 111     111 111 111
         +     111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111
        0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  PERCEN-   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
   TILES    0   0   0   2   5  11  18  30  39  48  60  69  83  86  91  92  95  97 100
            +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
         -5.393  -4.393  -3.393  -2.393  -1.393  -0.393   0.607   1.607   2.607   3.607
             -4.893  -3.893  -2.893  -1.893  -0.893   0.107   1.107   2.107   3.107

                    INTERVAL ENDPOINTS (UNITS OF 1.0E -6)
```

The Average Daily Change in the Hemoglobin Concentration.

```
MEAN =   5.197E-07,   STD. DEVIATION =  2.606E-04,   N =    105

      20++
         +
         +                         111
         +                         111
         +                         111     111
      15++                         111     111
         +                         111     111
C        +                     111 111     111
O        +                     111 111 111 111
U        +                     111 111 111 111
N     10++                     111 111 111 111 111 111
T        +                     111 111 111 111 111 111
         +                     111 111 111 111 111 111
         +             111     111 111 111 111 111 111
         +             111     111 111 111 111 111 111
       5++         111 111 111 111 111 111 111 111 111
         +         111 111 111 111 111 111 111 111 111 111
         +         111 111 111 111 111 111 111 111 111 111
         +     111 111 111 111 111 111 111 111 111 111 111
         + 111 111 111 111 111 111 111 111 111 111 111 111 111 111
       0++ ++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-    +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
 TILES     0   0   2   7  14  19  31  48  60  75  84  94  98  99 100
           +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
  -7.069  -5.069  -3.069  -1.069   0.931   2.931   4.931   6.931
      -6.069  -4.069  -2.069  -0.069   1.931   3.931   5.931

         INTERVAL ENDPOINTS (UNITS OF 1.0E -4)
```

The Average Daily Change in the Erythrocyte Count.

```
 MEAN = -8.339E-05,  STD. DEVIATION =  3.297E-04,  N =    86

      20++
         +
         +                                              111
         +                                         111  111
         +                                         111  111
      15++                                         111  111
         +                                         111  111
C        +                                         111  111
O        +                                    111  111  111
U        +                                    111  111  111
N     10++                                    111  111  111
T        +                                    111  111  111
         +                                    111  111  111
         +                                    111  111  111
         +                          111       111  111  111  111       111
       5++                          111       111  111  111  111       111  111
         +                          111  111  111  111  111  111       111  111  111
         +                          111  111  111  111  111  111  111  111  111  111
         +                          111  111  111  111  111  111  111  111  111  111
         +                111       111  111  111  111  111  111  111  111  111  111       111  111
       0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +
 TILES     2    2    2    2    3    3   10   15   29   48   69   76   80   87   93   97   97   98  100
           +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +    +
       -1.007    -0.807    -0.607    -0.407    -0.207    -0.007     0.193     0.393     0.593     0.793
            -0.907    -0.707    -0.507    -0.307    -0.107     0.093     0.293     0.493     0.693

             INTERVAL ENDPOINTS (UNITS OF 1.0E -3)

OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE      9
               OBS. NUMBER     39, NAME '        ', IS -0.001573.
               OBS. NUMBER     78, NAME '        ', IS -0.001061.
```

The Average Daily Change in the Leucocyte Count.

```
   MEAN = -3.160E-01,  STD. DEVIATION =  5.559E-01,   N =    105
       20++
          +
          +                     111
          +                     111         111
          +                     111         111
       15++                     111         111
          +                     111         111
 C        +                     111         111 111
 O        +                     111         111 111 111
 U        +                     111         111 111 111
 N     10++                     111         111 111 111
 T        +                 111 111         111 111 111
          +             111 111 111         111 111 111
          +             111 111 111 111 111 111 111 111
          +             111 111 111 111 111 111 111 111
        5++             111 111 111 111 111 111 111 111
          +             111 111 111 111 111 111 111 111 111
          +         111 111 111 111 111 111 111 111 111 111
          +     111 111 111 111 111 111 111 111 111 111 111 111
          +  111 111 111 111 111 111 111 111 111 111 111 111 111 111
        0++ ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
 PERCEN-    +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
  TILES     0   0   1   3   6  14  22  40  46  62  75  86  93  97  99 100
            +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
        -1.900  -1.500  -1.100  -0.700  -0.300   0.100   0.500   0.900
            -1.700  -1.300  -0.900  -0.500  -0.100   0.300   0.700   1.100

                INTERVAL ENDPOINTS


 OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     11
            OBS. NUMBER      7, NAME '        ', IS -1.965.
```

The Average Daily Change in the Neutrophil Count.

```
MEAN = -1.810E-01,  STD. DEVIATION =  4.370E-01,  N =   105

       15++
         +                                          111
         +                                          111
         +                                          111
         +                                      111 111     111 111
C      10++                                     111 111     111 111
O        +                                      111 111     111 111
U        +                                      111 111     111 111
N        +                                      111 111     111 111 111
T        +                      111         111 111 111 111 111 111 111 111
        5++                     111 111     111 111 111 111 111 111 111 111
         +                      111 111     111 111 111 111 111 111 111 111
         +                  111 111 111     111 111 111 111 111 111 111 111 111 111
         +      111         111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111
         +      111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111     111
        0++ ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-     +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
 TILES      0   0   2   3   4   7   13  18  20  25  36  49  55  65  76  82  88  91  94  96  98  98  99  99
            +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
          -1.300  -1.100  -0.900  -0.700  -0.500  -0.300  -0.100   0.100   0.300   0.500   0.700   0.900
              -1.200  -1.000  -0.800  -0.600  -0.400  -0.200   0.000   0.200   0.400   0.600   0.800   1.000

              INTERVAL ENDPOINTS

OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     12
                 OBS. NUMBER     97, NAME '        ', IS -1.303.
                 OBS. NUMBER     98, NAME '        ', IS  1.052.
```

The Average Daily Change in the Non-filamented Neutrophil Count.

```
MEAN = -2.929E-02,  STD. DEVIATION =  3.022E-02,  N =   105

   20++
      +
      +                                     111
      +                                     111
      +                             111 111 111
   15++                             111 111 111
      +                             111 111 111
C     +                             111 111 111
O     +                             111 111 111
U     +                         111 111 111 111
N  10++                         111 111 111 111
T     +                         111 111 111 111 111 111
      +                     111 111 111 111 111 111 111
      +                     111 111 111 111 111 111 111
      +                     111 111 111 111 111 111 111
    5++                 111 111 111 111 111 111 111 111
      +                 111 111 111 111 111 111 111 111
      +         111 111 111 111 111 111 111 111 111 111
      +         111 111 111 111 111 111 111 111 111 111     111
      +         111 111 111 111 111 111 111 111 111 111 111 111
    0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-  +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
 TILES   1   1   1   4   7  12  20  30  45  60  78  86  95  96  98  98  99
         +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
   -1.100  -0.900  -0.700  -0.500  -0.300  -0.100   0.100   0.300   0.500
       -1.000  -0.800  -0.600  -0.400  -0.200  -0.000   0.200   0.400

           INTERVAL ENDPOINTS (UNITS OF 1.0E -1)

OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE    13
            OBS. NUMBER     7, NAME '        ', IS -0.1506.
            OBS. NUMBER    21, NAME '        ', IS  0.05471.
            OBS. NUMBER    66, NAME '        ', IS -0.1141.
            OBS. NUMBER    70, NAME '        ', IS  0.06423.
```

The Average Daily Change in the Eosinophil Count.

```
MEAN = -1.190E-02,  STD. DEVIATION =  6.025E-02,  N =   105

      30++
         +
         +
         +
         +                                111
      25++                                111
         +                                111 111
         +                                111 111
         +                                111 111
         +                                111 111
      20++                                111 111
         +                                111 111
  C      +                                111 111
  O      +                                111 111
  U      +                                111 111
  N   15++                                111 111
  T      +                            111 111 111
         +                            111 111 111 111
         +                            111 111 111 111
         +                            111 111 111 111
      10++                        111 111 111 111 111
         +                        111 111 111 111 111
         +                        111 111 111 111 111
         +                        111 111 111 111 111
         +                        111 111 111 111 111
       5++                        111 111 111 111 111
         +                        111 111 111 111 111 111
         +                    111 111 111 111 111 111 111
         +                    111 111 111 111 111 111 111 111 111
         +  111 111         111 111 111 111 111 111 111 111 111 111
       0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
 PERCEN-    +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
  TILES     2   3   4   4   4   5   8  18  31  56  79  91  95  97  99  99  99
            +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
        -1.800  -1.400  -1.000  -0.600  -0.200   0.200   0.600   1.000   1.400
            -1.600  -1.200  -0.800  -0.400  -0.000   0.400   0.800   1.200

              INTERVAL ENDPOINTS (UNITS OF 1.0E -1)

OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     14
               OBS. NUMBER      7, NAME '        ', IS -0.1967.
               OBS. NUMBER     18, NAME '        ', IS -0.1905.
               OBS. NUMBER     70, NAME '        ', IS  0.1566.
               OBS. NUMBER     97, NAME '        ', IS -0.3540.
```

The Average Daily Change in the Basophil Count.

```
 MEAN = -4.341E-03,  STD. DEVIATION =  1.749E-02,  N =   105

      20++                                     111
         +                                     111
         +                                     111
         +                                     111
         +                                 111 111
      15++                                 111 111
         +                                 111 111
C        +                                 111 111
O        +                                 111 111
U        +                                 111 111
N     10++                                 111 111 111
T        +                                 111 111 111 111
         +                         111     111 111 111 111
         +                         111     111 111 111 111     111
         +                         111     111 111 111 111 111 111
       5++                 111     111     111 111 111 111 111 111
         +             111 111     111 111 111 111 111 111 111 111
         +         111 111 111 111 111 111 111 111 111 111 111 111         111
         +     111 111 111 111 111 111 111 111 111 111 111 111 111 111     111
         +     111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111
       0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-    +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
 TILES     0   0   2   5   9   14  17  24  28  43  62  72  80  86  93  95  96  99  100
           +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
       -5.000  -4.000  -3.000  -2.000  -1.000  -0.000   1.000   2.000   3.000   4.000
           -4.500  -3.500  -2.500  -1.500  -0.500   0.500   1.500   2.500   3.500

              INTERVAL ENDPOINTS (UNITS OF 1.0E -2)


OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     15
               OBS. NUMBER     74, NAME '        ', IS -0.05292.
```

The Average Daily Change in the Lymphocyte Count.

```
MEAN = -4.311E-02,  STD. DEVIATION =  1.850E-01,  N =   105
       15++
          +                                     111
          +                         111         111
          +                         111         111             111
          +                         111     111 111             111
C      10++                         111     111 111             111
O         +                         111     111 111             111
U         +                     111 111 111 111 111             111 111
N         +                     111 111 111 111 111         111 111 111
T         +                     111 111 111 111 111 111 111 111 111
        5++                     111 111 111 111 111 111 111 111 111
          +                     111 111 111 111 111 111 111 111 111 111
          +                     111 111 111 111 111 111 111 111 111 111
          +                 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111
          +     111 111     111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111
        0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-     +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
 TILES      0   0   0   1   1   3   11  23  31  41  55  60  67  79  86  90  92  94  96  98  99
            +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
          -5.500  -4.500  -3.500  -2.500  -1.500  -0.500   0.500   1.500   2.500   3.500   4.500
              -5.000  -4.000  -3.000  -2.000  -1.000   0.000   1.000   2.000   3.000   4.000

                   INTERVAL ENDPOINTS (UNITS OF 1.0E -1)

OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     16
               OBS. NUMBER    43, NAME '       ', IS  0.4739.
```

The Average Daily Change in the Monocyte Count.

```
MEAN = -7.133E-02,  STD. DEVIATION =  7.249E-02,  N =   105

      15++
         +                                              111
         +                              111             111
         +                              111             111
         +                              111             111
C     10++                              111         111 111
O        +                              111 111     111 111     111
U        +                      111 111 111 111     111 111     111
N        +                      111 111 111 111     111 111 111 111
T        +                      111 111 111 111 111 111 111 111 111
       5++              111     111 111 111 111 111 111 111 111 111
         +              111     111 111 111 111 111 111 111 111 111     111
         +              111 111 111 111 111 111 111 111 111 111 111 111 111
         +              111 111 111 111 111 111 111 111 111 111 111 111 111             111
         +  111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111 111     111
       0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-    +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
 TILES     0   0   1   2   7  10  18  25  38  46  52  61  75  81  90  93  97  98  98 100
           +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
        -2.600  -2.200  -1.800  -1.400  -1.000  -0.600  -0.200   0.200   0.600   1.000
            -2.400  -2.000  -1.600  -1.200  -0.800  -0.400  -0.000   0.400   0.800   1.200

                INTERVAL ENDPOINTS (UNITS OF 1.0E -1)
```

The Average Daily Change in the Platelet Count.

```
        MEAN = -1.528E-06,   STD. DEVIATION =  2.672E-05,   N =   105

     100++                                          111
         +                                          111
         +                                          111
         +                                          111
         +                                          111
      75++                                          111
         +                                          111
  C      +                                          111
  O      +                                          111
  U      +                                          111
  N   50++                                          111
  T      +                                          111
         +                                          111
         +                                          111
         +                                          111
      25++                                          111
         +                                          111
         +                                          111
         +                                          111
         +      111      111                        111      111 111          111
       0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  PERCEN-  +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
   TILES   1   1   2   2   3   3   3   3   96  96  97  98  98  98  99
           +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
       -7.068  -5.068  -3.068  -1.068   0.932   2.932   4.932   6.932
           -6.068  -4.068  -2.068  -0.068   1.932   3.932   5.932

               INTERVAL ENDPOINTS (UNITS OF 1.0E -5)


 OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     18
               OBS. NUMBER    41, NAME '        ', IS -0.2225E-03.
               OBS. NUMBER    49, NAME '        ', IS -0.7345E-04.
               OBS. NUMBER    61, NAME '        ', IS  0.9683E-04.
```

The Average Daily Change in the Atypical Erythrocyte Count.

MEAN = 1.233E-06, STD. DEVIATION = 1.295E-05, N = 105

```
        100++
            +                                 111
            +                                 111
            +                                 111
            +                                 111
         75++                                 111
            +                                 111
  C         +                                 111
  O         +                                 111
  U         +                                 111
  N      50++                                 111
  T         +                                 111
            +                                 111
            +                                 111
            +                                 111
         25++                                 111
            +                                 111
            +                                 111
            +                                 111
            +                  111 111        111                      111 111
          0++  +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
  PERCEN-      +    +    +    +    +    +    +    +    +    +    +    +    +    +    +
   TILES       1    1    1    1    3    4    4    94   94   94   94   94   95   97   97
               +    +    +    +    +    +    +    +    +    +    +    +    +    +    +
           -3.349    -2.349    -1.349    -0.349     0.651     1.651     2.651     3.651
                -2.849    -1.849    -0.849     0.151     1.151     2.151     3.151

                   INTERVAL ENDPOINTS (UNITS OF 1.0E -5)


OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     19
                   OBS. NUMBER     48, NAME '         ', IS  0.7255E-04.
                   OBS. NUMBER     65, NAME '         ', IS  0.4162E-04.
                   OBS. NUMBER     80, NAME '         ', IS -0.4308E-04.
                   OBS. NUMBER     89, NAME '         ', IS -0.3873E-04.
                   OBS. NUMBER    102, NAME '         ', IS  0.6890E-04.
```

The Average Daily Change in the Atypical Platelet Count.

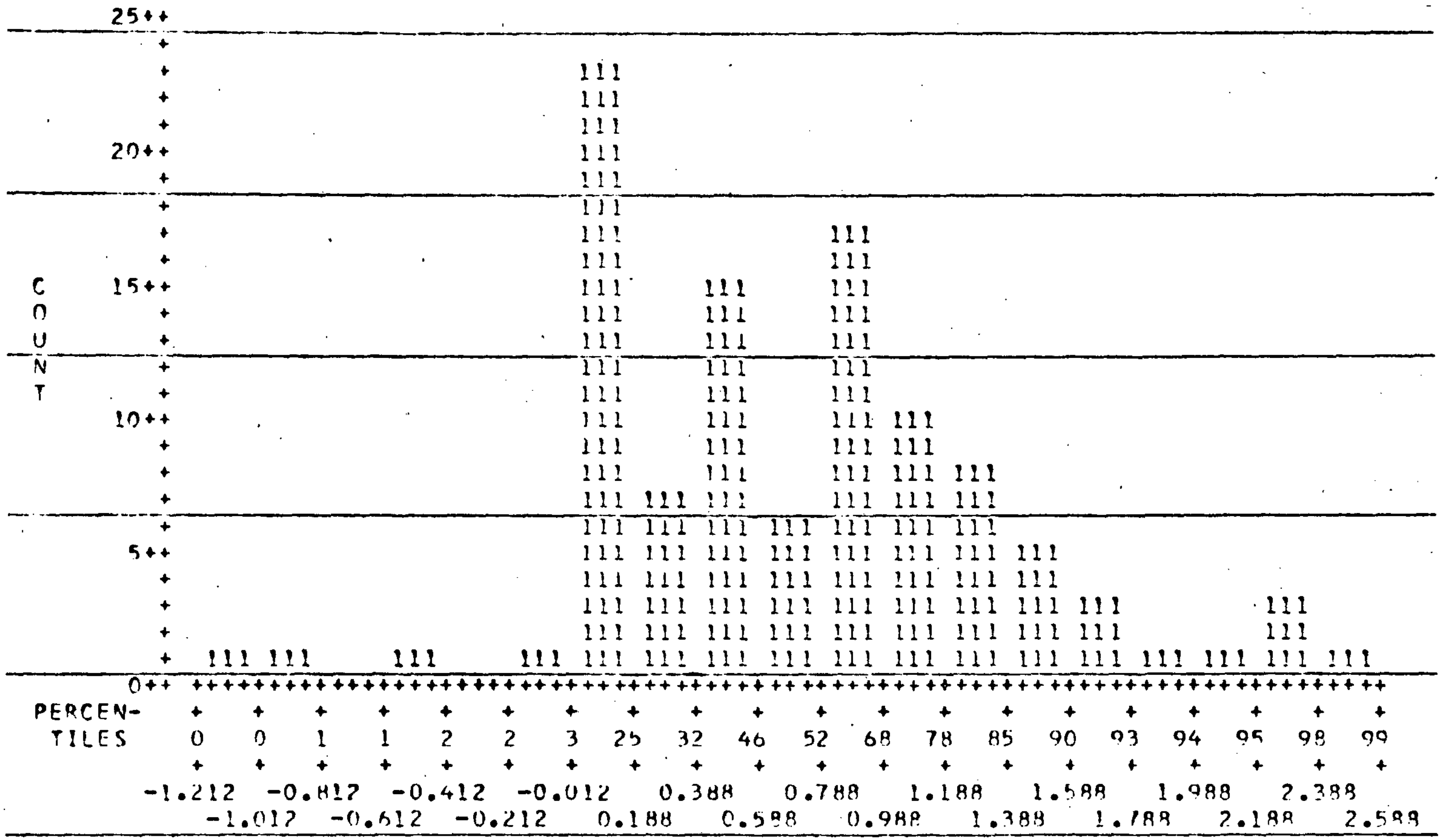
```
      MEAN =  1.446E-05,  STD. DEVIATION =  3.869E-05,  N =   105
   100++
       +
       +                                111
       +                                111
       +                                111
    75++                                111
       +                                111
C      +                                111
O      +                                111
U      +                                111
N   50++                                111
T      +                                111
       +                                111
       +                                111
       +                                111
    25++                                111
       +                                111
       +                                111
       +                                111
       +                            111 111                 111 111 111 111 111 111 111 111
     0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
PERCEN-   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
 TILES    0   0   0   0   0   0   0   0   0   0  84  84  84  84  85  88  90  91  93  94  96  97
          +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
      -0.907  -0.707  -0.507  -0.307  -0.107   0.093   0.293   0.493   0.693   0.893   1.093
          -0.807  -0.607  -0.407  -0.207  -0.007   0.193   0.393   0.593   0.793   0.993   1.193

              INTERVAL ENDPOINTS (UNITS OF 1.0E -4)


OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     20
              OBS. NUMBER    27, NAME '        ', IS  0.1527E-03.
              OBS. NUMBER    64, NAME '        ', IS  0.1976E-03.
              OBS. NUMBER    96, NAME '        ', IS  0.1914E-03.
```

The Average Daily Change in the Atypical Lymphocyte Count.

MEAN = 7.328E-05, STD. DEVIATION = 6.982E-05, N = 105



INTERVAL ENDPOINTS (UNITS OF 1.0E -4)

OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE 21
OBS. NUMBER 88, NAME ' ', IS 0.3020E-03.

The Average Daily Change in the Count of Other Atypical Leucocytes.

```
        MEAN =  4.511E-06,  STD. DEVIATION =  2.655E-05,  N =   105

      100++
           +                          111
           +                          111
           +                          111
           +                          111
       75++                           111
           +                          111
 C         +                          111
 O         +                          111
 U         +                          111
 N     50++                           111
 T         +                          111
           +                          111
           +                          111
           +                          111
       25++                           111
           +                          111
           +                          111
           +                          111
           +           III            111    III III    III III
        0++ +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
 PERCEN-    +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
 TILES      1   1   1   2   2   2   2   2  91  91  92  93  93  94  95  95
            +   +   +   +   +   +   +   +   +   +   +   +   +   +   +   +
        -7.068  -5.068  -3.068  -1.068   0.932   2.932   4.932   6.932
            -6.068  -4.068  -2.068  -0.068   1.932   3.932   5.932   7.932

                 INTERVAL ENDPOINTS (UNITS OF 1.0E -5)


 OBSERVATION(S) OUTSIDE RANGE OF ABOVE PLOT, ON VARIABLE     22
               OBS. NUMBER     26, NAME '        ', IS  0.1010E-03.
               OBS. NUMBER     32, NAME '        ', IS -0.7079E-04.
               OBS. NUMBER     61, NAME '        ', IS  0.9381E-04.
               OBS. NUMBER     62, NAME '        ', IS  0.1385E-03.
               OBS. NUMBER     88, NAME '        ', IS -0.9128E-04.
               OBS. NUMBER     96, NAME '        ', IS  0.8095E-04.
               OBS. NUMBER     98, NAME '        ', IS  0.8805E-04.
```