### Title
HEMATOLOGIC EFFECTS IN MAN OF LOW-LEVEL RADIATION EXPOSURE




### Authors
Dobson, R. Lowry.
Chupp, Mary M.



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# UNIVERSITY OF CALIFORNIA

# *Radiation Laboratory*



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## DISCLAIMER

# HEMATOLOGIC EFFECTS IN MAN OF LOW-LEVEL RADIATION EXPOSURE*,†

R. L. Dobson§ and M. M. Chupp

## I. INTRODUCTION

Very little direct information is available on the effects in man of small doses of ionizing radiation. Present concepts are based largely on extrapolation from higher doses in humans and from experiments on animals. The need for studies of effects on human beings of small doses or of chronic low-level exposure to ionizing radiation is apparent.

The particular sensitivity of the blood-forming organs to x-rays was demonstrated by Heineke as early as 1903 (1, 2). Many investigators since then have described changes in the peripheral blood, especially depressions of the cellular elements. Jacobson, in reviewing the hematologic effects of ionizing radiation (3), points out that few observations have been reported during the last twenty years which had not previously appeared in reports of early workers such as Heineke (2), Russ, et al. (4), Lacassagne and Levadan (5), and others.

Until the early 1940's most studies of radiation-induced changes in hemopoietic tissue and blood were with relatively large doses of ionizing radiation. Human data came only from accidental exposures (6, 7) and from patients receiving radiation therapy (8, 9). The development of the atomic energy program gave impetus to studies on effects of small doses and chronic low-level exposure; however, there have been only a few convincing quantitative studies on man.

The most suggestive effects described in human beings are minimal changes in leukocyte count and morphology. Sievert and Helde observed changes in persons exposed to x-rays at levels estimated to be as low as 0.02 r to 0.05 r per day (10, 11). Mayneord reported a significant depression in

*Donner Laboratory of Biophysics and Medical Physics, University of California, Berkeley, California.

†With contributions by Dr. Harley B. Messinger and Dr. Nicholas L. Petrakis, Department of Preventive Medicine, University of California School of Medicine, San Francisco, California.

§Present address: World Health Organisation, Palais des Nations, Geneva, Switzerland.

leukocytes in persons exposed to levels presumably not greatly exceeding 0.125 r per week (12). Knowlton found a statistically significant gradual decline in the absolute lymphocyte counts in a group of persons chronically exposed to gamma radiation at an average level of 0.21 r per week (13). Morphologic changes in lymphocytes were observed by Ingram and Barnes, who reported an increased incidence of bilobed and binucleated lymphocytes in the circulating blood of cyclotron workers exposed to presumably very low levels of irradiation (14). Subsequent studies with dogs (15) and more detailed observations on humans (16) seemed to confirm the original findings.

When Ingram's observations came to our attention, a number of experiments were carried out at this laboratory to investigate this phenomenon(17). The results suggested that indeed there was an increase in the incidence of binucleated lymphocytes (BnL) in individuals exposed intermittently or chronically to radiation at levels below 0.3 r per week. These data, however, were not sufficiently complete to allow adequate statistical evaluation. Peripheral blood studies were subsequently undertaken. The nature and magnitude of the BnL response were studied in normal human beings exposed to (a) chronic low-level radiation and (b) single isolated doses of ionizing radiation. A significant inceease in the incidence of BnL was observed in persons whose average yearly exposure was in the range of only 0.1 to 0.2 r per week, as well as in persons exposed to single isolated doses of ionizing radiation at about 2.5 r.

The desoxyribonucleic acid (DNA) content of the BnL was also studied. Results indicate that these cells contain probably the normal lymphocyte complement of DNA.

## II. METHODS

### CHRONIC EXPOSURE STUDY

Binucleated lymphocytes (BnL) were counted in the peripheral blood of fifteen normal individuals. Comparison was made between a group exposed to low-level irradiation and a normal control group. The former was made up of eight healthy young men receiving, in the course of their work as accelerator operators, intermittent and chronic exposures of predominantly x and gamma radiation. The control group was made up of seven persons receiving no known exposures to radiation above background levels. The two groups were approximately matched by age.

Determinations of the doses received by persons in the exposed group were made by daily electroscope readings and weekly film-badge measurements. Average exposures for the year, the month, and the week prior to the experiment were computed for each person as well as for the group as a whole (Table I). Weekly neutron exposures were determined from track counts on neutron-sensitive film badges. On the basis of an assumed relative biological effectiveness of 10 for neutrons, the yearly average dose received by one subject (C-1) amounted to 0.04 rem per week from neutrons in addition to the dose listed in Table I. The other subjects received an average of from 0.01 to 0.02 rem per week from neutrons. There were no positive film-badge readings in the control group.

For the BnL counts, samples of capillary blood were taken from the ear lobe at hourly intervals for five or more consecutive hours on the day of sampling. No anticoagulants or concentration methods were used. Fresh blood films were treated with Wright's stain. The slides were examined at 200 X magnification with a microscope provided with a mechanically driven stage. The total numbers of white blood cells and BnL seen were recorded. Only BnL with two completely separate nuclei or with two nonoverlapping nuclei connected by a thin hairlike filament (Fig. 1) were recorded. Cells not meeting these criteria and cells with bilobed nuclei were not considered in this study. On each slide, 6,000 to 10,000 white blood cells were counted. Positional coordinates for each BnL were recorded.

In an attempt to explore the time sequence of the BnL response and to observe possible changes due to single or cumulative exposures, detailed studies were made on two individuals, over a period of several months in one case and over almost two years in the other. Daily electroscope records were maintained for the whole experimental period and were checked with weekly film-badge readings for consistency. Neutron exposures were measured as described above.

## ACUTE EXPOSURE STUDY

A group of seven healthy individuals working at the Nevada Test Site during an operational period was chosen for study. Selection of these persons was based on the nature of their assignment, which was the measurement of certain radiation levels at the site. In the course of this work each individual received a single total-body exposure of gamma radiation in a period of 15 to 30 minutes. In each case the magnitude of the exposure was determined from three film badges and checked with pocket electroscopes and portable meters. Beta radiation was negligible, and neutrons did not contribute to the dose.

Medical examinations, complete blood counts, and urinalyses were done to rule out the existence of complicating abnormalities. To exclude the possibility that internal radiation might be contributing to the dose, scintillation counting over the thyroid area was carried out and radio-assay studies for alpha and beta emitters in 24-hour urine samples were performed before and after exposure, with negative results. It was established that none of these persons had undergone any diagnostic x-ray examination for at least 6 months prior to the experiment. Film-badge records covering a period of 6 months prior to the study did show, however, that most of these individuals had received some radiation exposure during the preceding half year. These data are presented in Table II.

Hematological studies were conducted during a control period prior to exposure and for 11 days after exposure. On each person, five blood counts were taken daily at 2-hour intervals for a period of 3 days before exposure. The same procedure was followed on the day of exposure and on the first, second, fourth, sixth, ninth, tenth, and eleventh postexposure days. Blood films for differential counts were made from capillary blood

TABLE I

Average radiation exposures in r per week during three precount intervals

| Subject | Year preceding count | Month preceding count | Week preceding and including days of count |
|---|---|---|---|
| C-1 | .12 | .05 | .15 |
| C-2 | .15 | .22 | .18 |
| C-3 | .04 | .09 | .16 |
| C-4 | .04 | .04 | .16 |
| C-5 | .08 | .12 | .38 |
| C-6 | .13 | .16 | .28 |
| C-7 | .17 | .1 | .09 |
| C-8 | .15 | .21 | .12 |
| Mean | .11 | .12 | .19 |

TABLE II

Exposures (in r) received during the six months preceding the experiment (April to September 1957)

| Subject | April | May | June | July | August | September | Total |
|---|---|---|---|---|---|---|---|
| A-1 | .16 | 0 | 0 | 0 | 0 | 0 | .16 |
| A-2 | 0 | 0 | 0 | 0 | 0 | .08 | .08 |
| A-3 | 0 | .06 | .09 | 0 | .05 | .40 | .60 |
| A-4 | 0 | 0 | 0 | .1 | .12 | .13 | .35 |
| A-5 | 0 | 0 | 0 | 0 | 0 | .40 | .40 |
| A-6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| A-7 | - | .02 | 0 | 0 | 0 | 0 | .02 |

samples obtained by ear puncture at 8:00 a.m., 10:00, 12:00, 2:00 p.m., and 4:00. Blood films were treated with Wright's stain. Total leukocyte counts in duplicate were done at 8:00 a.m., noon, and 4:00 p.m.

To avoid possible bias, a different worker independently coded the slides with random numbers before they were examined. BnL and total white cells were counted and recorded as described above.

## LYMPHOCYTE DNA CONTENT

The total DNA content of eight BnL and of the individual "nuclei" was determined by Feulgen microspectrophotometry on blood smears by use of a method described by Petrakis and Folstad (18). The DNA content of normal lymphocytes on the same slide was measured for control.

# III. RESULTS

## CHRONIC EXPOSURE STUDY

Results of the comparative study on the chronically exposed and unexposed groups are presented in Table III and in Fig. 2. These data were derived from the counting of more than one million white blood cells. It is apparent that the incidence of binucleated lymphocytes (BnL) among the circulating white cells is very low, and that it was higher in the exposed than in the unexposed group. The mean in the control group was 1.4 BnL per 50,000 leukocytes, with a range of 0.4 to 2.5; it was 5.9 per 50,000 in the exposed group, with a range of 3.4 to 7.6.

The suggestion of a pattern of response to individual doses of radiation is seen in Fig. 3, where daily exposures of still another person are shown, with scattered BnL counts for a period of 90 days. The daily radiation exposures, which were predominantly gamma radiation, varied from 0 to 0.26 r. The incidence of BnL over the period of 3 months fluctuated from 0 to 10 per 50,000 white blood cells. The larger numbers seemed to appear several days after individual exposure to 0.2 r or more. Daily counts were taken during the last 10 days of observation following a dose of 0.26 r. Two days after this exposure the incidence of BnL was 15 per 50,000 white blood cells; 10 days after exposure it was 17 per 50,000. Between times the incidence varied from 1 to 8. Thus, there was suggested a biphasic pattern of response with peaks at about 2 days and again at about 10 days after an individual exposure.

Data collected over a 21-month period from another individual are presented in Fig. 4. This person had worked with radiation for many years. It is worthy of note that the incidence of BnL was maintained at a high level for the entire period of observation, and did not decrease during a 3-month interval while the subject received essentially no radiation exposure. The average incidence of BnL in this man is higher than we have observed in most exposed persons. This may represent individual variation. The striking peak of 21 per 50,000 followed upon several successive exposures of from 0.2 to 0.4 r.

TABLE III

The incidence of binucleated lymphocytes among white cells in the peripheral blood of normal persons chronically exposed to low-level x- and gamma radiation and the incidence in unexposed persons.

| Subject | Age | Number of hourly samples | Number of leukocytes counted | Number of binucleated lymphocytes seen | Calculated number of binucleated lymphocytes per 50,000 white cells |
|---|---|---|---|---|---|
| | | | **Exposed Group** | | |
| C-1 | 31 | 6 | 58,172 | 8 | 6.9 |
| C-2 | 23 | 11 | 106,000 | 16 | 7.6 |
| C-3 | 35 | 6 | 60,000 | 9 | 7.5 |
| C-4 | 29 | 6 | 60,000 | 5 | 4.2 |
| C-5 | 39 | 6 | 60,000 | 4 | 3.4 |
| C-6 | 29 | 5 | 50,000 | 7 | 7.0 |
| C-7 | 26 | 5 | 39,000 | 4 | 5.0 |
| C-8 | 34 | 5 | 34,700 | 4 | 5.8 |
| Mean | 31 | Total 50 | Total 467,872 | Total 57 | Mean 5.9 $\sigma_M = 0.56$ |
| | | | **Control Group** | | |
| C-9 | 32 | 5 | 50,000 | 1 | 1.0 |
| C-10 | 29 | 8 | 80,000 | 3 | 1.9 |
| C-11 | 27 | 14 | 140,000 | 1 | 0.4 |
| C-12 | 27 | 6 | 60,000 | 3 | 2.5 |
| C-13 | 31 | 8 | 80,000 | 2 | 1.3 |
| C-14 | 29 | 7 | 70,000 | 3 | 2.2 |
| C-15 | 25 | 6 | 60,000 | 1 | 0.8 |
| Mean | 29 | Total 54 | Total 540,000 | Total 14 | Mean 1.4 $\sigma_M = 0.29$ |

## ACUTE EXPOSURE STUDY

Radiation doses received by the subjects as single exposures are presented in Table IV together with mean pre- and postexposure leukocyte counts. The total white blood cell counts in individuals as well as in the group as a whole did not change significantly after exposure.

In Table V are shown the BnL counts for the control period of two pre-exposure days and for two selected postexposure periods. Data from the third pre-exposure day, the day of exposure, and the fourth and sixth postexposure days are not available at this time. The first and second postexposure days were considered together as Period I, and the ninth, tenth, and eleventh postexposure days together as Period II. The incidence of BnL in the control period is seen to be rather higher than was observed in the first experiment.

Figure 5 is a graphical presentation of the difference in BnL incidence between the two postexposure periods and the control period. The subject who received 2.4 r showed a significant increase during the second post-exposure period, and the subject who received 2.6 r showed an increase during the first postexposure period. The errors shown in Fig. 5 are 1 standard deviation.

## LYMPHOCYTE DNA CONTENT

Measurements of the DNA content of eight BnL were compared with those of normal cells on the same slide. There was a considerable spread of the values found, but these early results strongly suggest that the total amount of DNA in the BnL is the same as in the normal lymphocytes, the diploid amount. Measurements on individual "nuclei" of the BnL gave values approximately one-half as great as those from normal cells.

## IV. DISCUSSION

The binucleated lymphocytes (BnL) appear to be Poisson-distributed among the white blood cells. This was tested with the data from the chronic-exposure study by the Chi-square variance test (19). The difference between the exposed and the unexposed groups, which is apparent from inspection of Fig. 2, was confirmed at the 1% significance level with a computed P value of 0.3%. The means for each group were also computed. The observed ratio (exposed/unexposed) of the means was 4.7, and the 95% confidence interval for the true ratio extended from 2.7 to 9.6.

Demonstration of the difference between these two groups provides strong support for the assumption that BnL response follows exposure to chronic low-level radiation. It is of special interest that the higher incidence of BnL was seen in a group of persons whose average weekly exposure was of the order of only 0.1 to 0.2 r.

The acute exposure study is, at this stage, somewhat less conclusive. However, the demonstration of an increase in BnL (by computation of the ratio of the means) at the 5% significance level in the two persons receiving doses of 2.4 and 2.6 r respectively, suggests a dose effect, since the

TABLE IV

Pre- and post-exposure leukocyte counts in seven normal individuals receiving single doses of gamma radiation

| Subject | Dose (r) | Pre-exposure mean total leukocyte count | | | Post-exposure mean total leukocyte count | | |
|---|---|---|---|---|---|---|---|
| | | 8:00 A.M. | 12:00 Noon | 4:00 P.M. | 8:00 A.M. | 12:00 Noon | 4:00 P.M. |
| A-1 | 0.7 | 7,660 | 9,256 | 9,285 | 7,475 | 8,807 | 9,312 |
| A-2 | 0.7 | 10,035 | 10,100 | 11,200 | 10,508 | 11,992 | 10,796 |
| A-3 | 1.4 | 8,856 | 8,894 | 10,075 | 9,303 | 10,615 | 9,650 |
| A-4 | 1.5 | 10,232 | 13,098 | 13,292 | 10,414 | 12,330 | 11,895 |
| A-5 | 1.7 | 12,194 | 11,231 | 10,975 | 13,781 | 12,007 | 12,928 |
| A-6 | 2.4 | 13,170 | 11,038 | 10,875 | 14,489 | 14,138 | 14,755 |
| A-7 | 2.6 | 10,912 | 10,632 | 10,763 | 10,365 | 10,695 | 12,547 |
| Mean | 1.5 | 10,437 | 10,598 | 10,924 | 10,905 | 11,512 | 11,412 |

## TABLE V

The incidence of binucleated lymphocytes (BnL) among leukocytes in the peripheral blood of seven normal persons before and after exposure to single doses of gamma radiation

| Subject | Dose (r) | Number of leukocytes counted | | | Number of BnL seen | | | Calculated number of BnL per 50,000 leukocytes | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Control Period | Period I[a] | Period II[b] | Control Period | Period I[a] | Period II[b] | Control Period | Period I[a] | Period II[b] |
| A-1 | 0.7 | 115,729 | 80,000 | 90,000 | 5 | 8 | 1 | 2.2 | 5.0 | 5.6 |
| A-2 | 0.7 | 136,331 | 90,000 | 110,000 | 12 | 9 | 9 | 4.4 | 5.0 | 4.1 |
| A-3 | 1.4 | 140,000 | 85,898 | 89,406 | 15 | 7 | 12 | 5.4 | 4.1 | 6.8 |
| A-4 | 1.5 | 140,000 | 90,000 | 110,000 | 12 | 13 | 9 | 4.3 | 7.2 | 4.1 |
| A-5 | 1.7 | 119,911 | 50,000 | 100,000 | 26 | 9 | 17 | 10.8 | 9.0 | 8.5 |
| A-6 | 2.4 | 152,382 | 90,000 | 100,000 | 10 | 14 | 21 | 3.3 | 7.8 | 10.5 |
| A-7 | 2.6 | 170,000 | 90,449 | 110,000 | 55 | 50 | 33 | 16.2 | 27.8 | 15.0 |

[a]First and second post-exposure days were considered together as Period I.

[b]Ninth, tenth, and eleventh post-exposure days were considered together as Period II.

persons receiving exposures less than 2 r failed to show a significant response. The fact that each of these two individuals showed a response at only one of the postexposure times indicates that caution should be used in connecting the BnL response to the radiation alone.

A factor of probable importance in the acute exposure study was the erratic pattern of daily living of all seven subjects during the period of observation. Their schedules of duties at this time were irregular; they frequently worked long hours and had very little sleep, meals also were irregular. It is not unlikely that these unusual living conditions were responsible for the high incidence of BnL seen during the control period. Furthermore, otherwise detectable responses to the smaller radiation doses may have been obscured.

The binucleated lymphocyte response is not specific to radiation. Murphy and Sturm reported seeing large numbers of these cells in the blood of animals after heat treatment (20). Ingram observed their increased incidence with various diseases, and has emphasized the importance of considering the general health of an individual when interpreting this hematological response (21). We have seen very high numbers of BnL in patients with lymphatic leukemia, and found their numbers elevated in infectious hepatitis and other conditions (22).

The pattern of lymphocyte response that is suggested in the 90-day observation period by peaks observed approximately 10 days after the highest exposures (Fig. 3) is interesting in relation to the early observations by Murphy and Sturm (20). In 1919 they described the appearance of binucleated lymphocytes in the peripheral blood of mice, rats, and guinea pigs 6 to 10 days after exposure to heat at temperatures of 55° to 65° C. The binucleated cells were most prominent at a time when regeneration of lymphoid tissues was maximal. Ingram reports the highest incidence of bilobed lymphocytes in dogs during the second 2 weeks after exposure to x-rays, and during the first 2 weeks after exposure to the environment of an operating cyclotron (15). Bellack and Storer observed the highest reponse peak in rats and mice approximately 1 week after irradiation (23).

The apparent nonspecificity and the time pattern of the response indeed make the original suggestion of Murphy and Sturm attractive--that these lymphocytes are cells in the midst of amitotic division, and are especially prevalent during periods of active lymphoid tissue repair following injury. Frank and Dougherty offer that this phenomenon is simply part of the general stress picture (24), and Dougherty suggests that the BnL might be expected to correlate with the large-diameter "stress lymphocyte" (25).

The DNA determinations indicated that these cells contain probably the usual lymphocyte complement of chromosomal material. This opposes the idea that they have been unable to complete their last mitosis; one would expect in that case to find a tetraploid amount of DNA present in the cell. Rather, these cells appear to have two "nuclei" dividing the diploid amount of DNA.

## SUMMARY

1. A significant increase in binucleated lymphocytes in the peripheral blood was observed in normal individuals exposed intermittently and chronically to low-level x and gamma radiation of the order of 0.1 to 0.2 r per week.

2. The average incidence of these cells in a group of eight chronically exposed persons was 5.9 per 50,000 leukocytes; the range was 3.4 to 7.6. The average incidence in a control group of seven persons was 1.4; the range was 0.4 to 2.5.

3. A significant increase in binucleated lymphocytes in the peripheral blood was observed in two normal individuals at different times after they were exposed to a single acute dose of gamma radiation of the order of 2.5 r.

4. Significant hematologic responses were not seen in five other normal individuals after single exposures to gamma radiation in doses less than 2 r.

5. The data presented suggest that peaks in the binucleated lymphocyte response pattern after individual doses of radiation occur within a few days to perhaps 10 days after exposure. In some individuals relatively high levels appear to persist.

6. The binucleated lymphocyte response is not specific to radiation. It is probably related also to physiologic stress.

7. A few measurements made of the DNA content of binucleated lymphocytes indicate that these cells contain probably the normal lymphocyte complement of DNA, divided between the two nuclei.

## ACKNOWLEDGMENT

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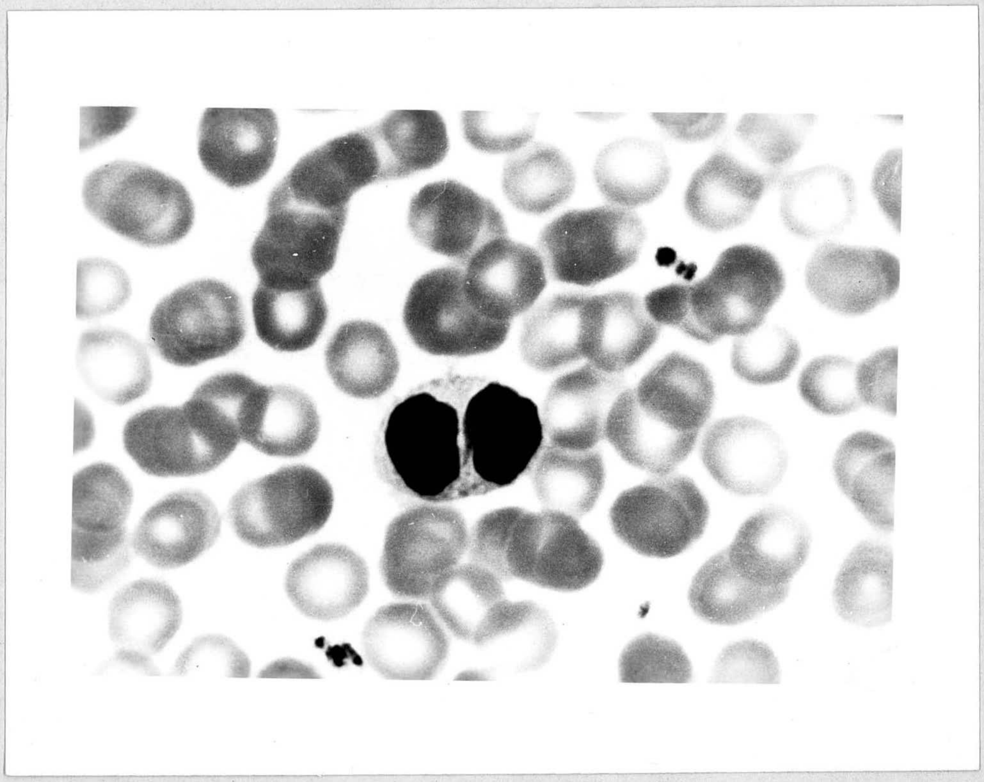

Fig. 1. Binucleated lymphocyte

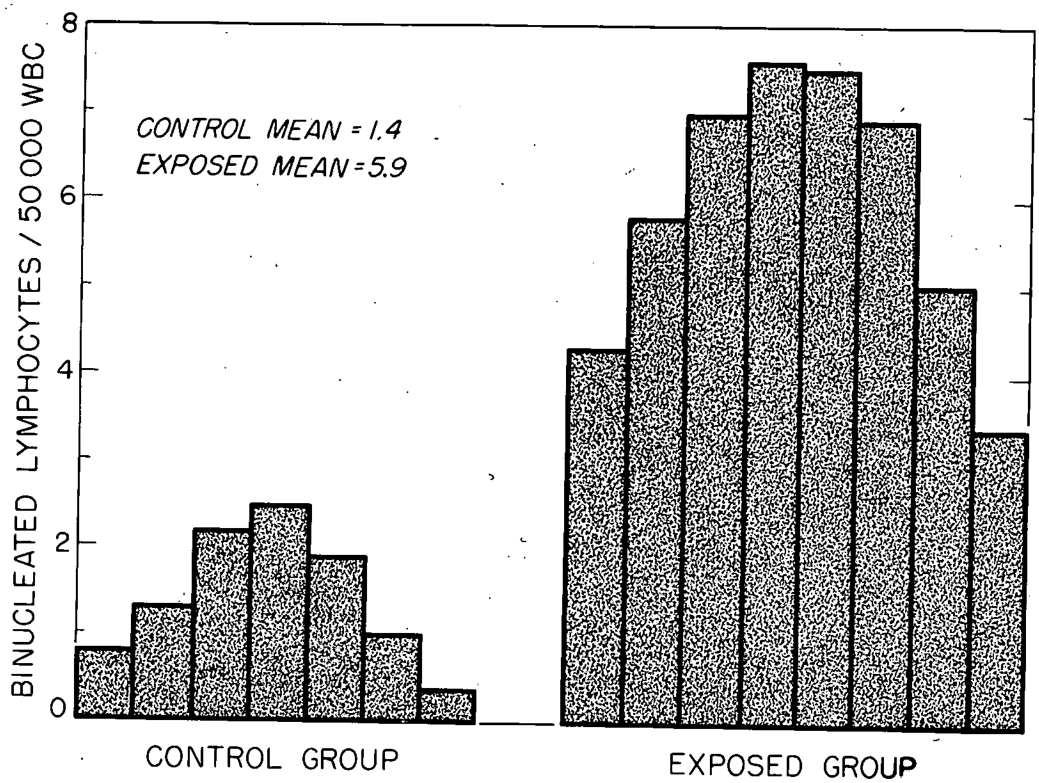


Fig. 2. Incidence of binucleated lymphocytes in the peripheral blood of 15 normal individuals: a comparison of the incidence in a group of persons exposed to low-level irradiation with incidence in an unexposed control group.

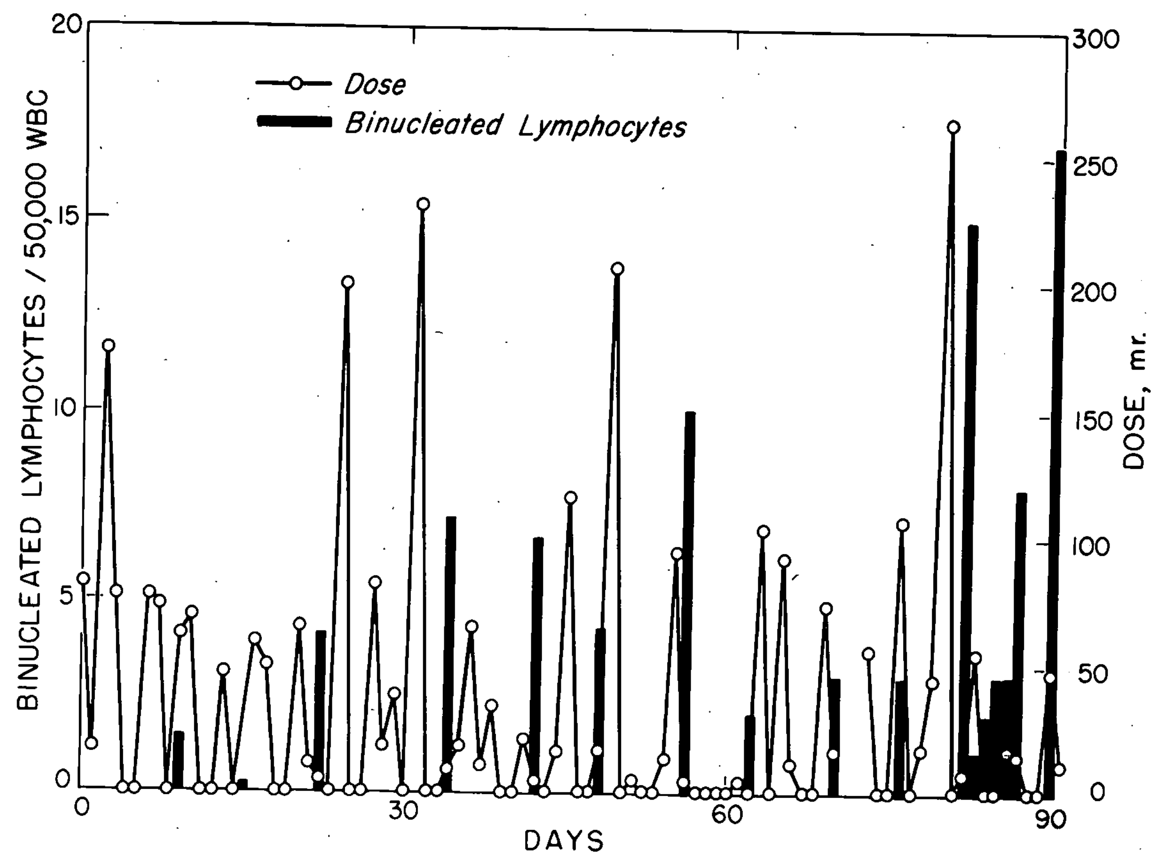


**Fig. 3. Daily radiation-dose record and periodic binucleated lymphocyte counts on one individual for a 90-day period.**

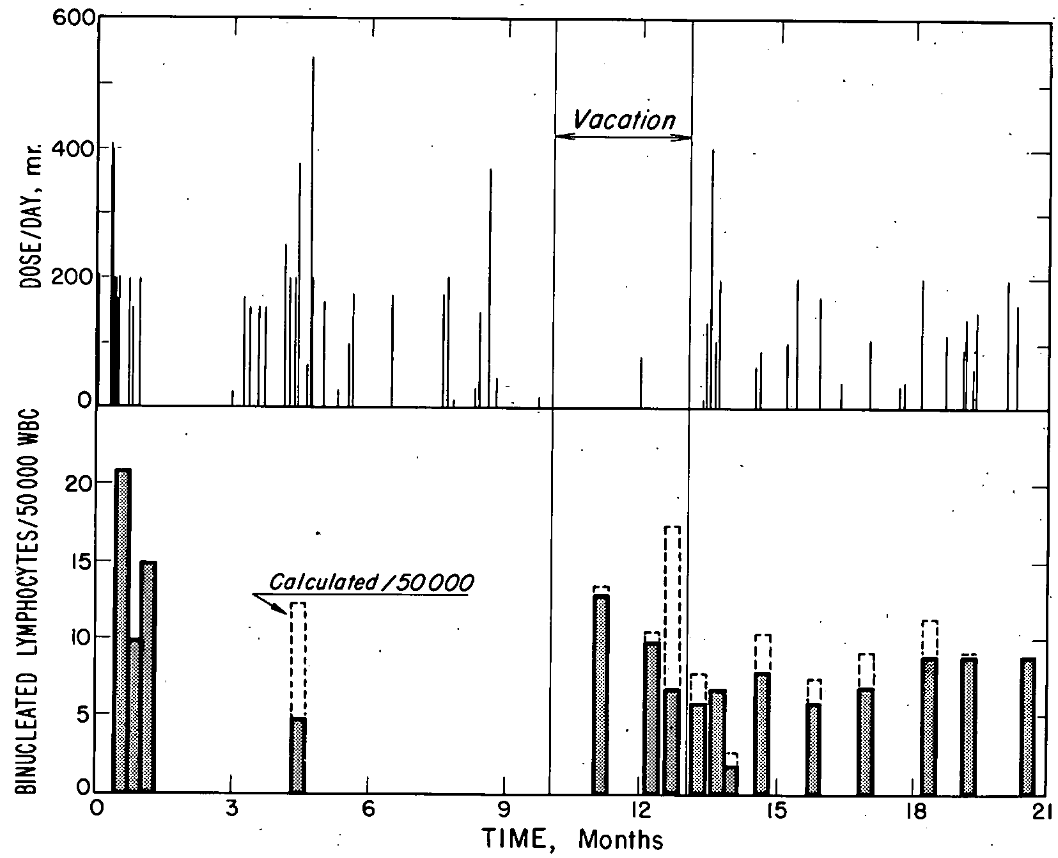


**Fig. 4. Radiation-dose record and periodic binucleated lymphocyte counts on one individual for a 21-month period.**

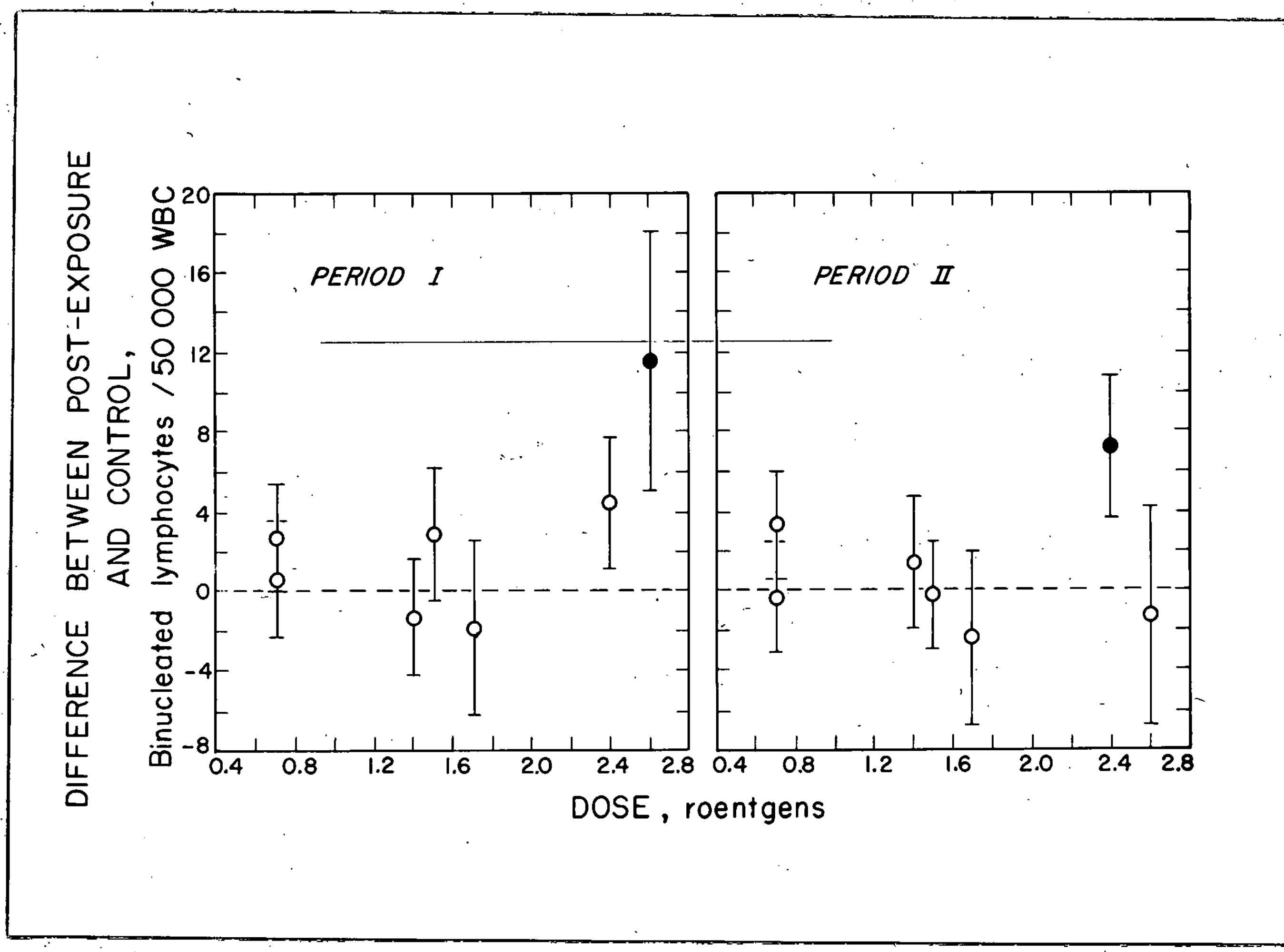


**Fig. 5. Mean differences in binucleated lymphocyte incidence between two postexposure periods and the control period.**

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