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ARGONNE NATIONAL LABORATORY
P.O. Box 5207
Chicago 80, Illinois

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X Ray and Statistics

George Sacher, Group Leader
Sylvanus Tyler

Time-series Investigation. Several years ago the hematology group inaugurated an experiment in which blood counts were taken on four members of the Health Division on every working day for a period of from one to two years. One of these subjects received a total body dose of 15 r given within two weeks after the series of counts started. The statistics group was confronted with the two problems:

1. What statistical deductions could be made about the behavior of the circulating white blood cells in terms of these data, and
2. In the light of the statistical properties of the series of counts, what could be asserted about the significance of an observed change in lymphocyte level of the one exposed subject.

This launched an extended and laborius investigation of these data. The results to be reported now are but a part of the statistical finding (in addition to the hematological findings to be reported by Dr. Jacobson). The findings so far fall under heading (1). We are not yet prepared to make statements about significance of changes, as in (2) above, in the present case, or for any data a formally similar nature from other experiments.

The analysis to be reported here is the results of autocorrelations calculated for the polymorphs and lymphocytes of two subjects. In an autocorrelation of lag k days the count of a given element of a given subject on day i is correlated with the count for the same element in the same subject for day $i + k + 1$, where i takes all values from $i = 1$ to $i = n - k - 1$, where n is the total number of daily counts. This procedure has received some development and application in economics but the present analysis is the first application in biology known to the writer.

When the autocorrelations are calculated for a number of lags, and the value of the correlation coefficient is plotted against the log interval, the resulting diagram is known as a correlogram. For the purposes of our work, we did not compute correlations, but rather the closely related quantities, covariances of lagged series. The covariance and the correlation stand in a linear relationship to each other, so that the shape of the curves presented below (Figures 1 or 2) is essentially the same as would appear for a correlogram. For the moment we will call our curves "self-lag variances diagrams".

The two curves of Figure 1 are the self-lag variances for the lymphocytes of two male subjects, ES and RF. The log intervals proceed in steps of one day for the first twenty days, and then in steps of five days to the sixtieth day. The ordinate scale (self-lag variance) increases from top to bottom because the variance decreases as the correlation coefficient increases.

The diagram show two kinds of behavior. There is a monotone increase in the magnitude of the log variance for about the first twenty days in both men (seen as a steady decline in Figure 1 because plotted upside-down). In addition there is a periodic behavior which is very pronounced for long intervals greater than twenty days. The waves signify the existence of periodicities in the variation of the lymphocyte level of circulating blood. In the diagram for ES, pronounced peaks can be seen at 25 and 45 days. Since 45 days is nearly an integral multiple of 25 days, we may conclude that there is not an independent period of 45 days, but rather a single pronounced periodicity of about 25 days. The diagram for RF is more complex, but clear evidence of periodicity may be seen here also. It will be necessary to extend the lag analysis in steps of

FIGURE I.

SELF LAG VARIANCES OF LYMPHS

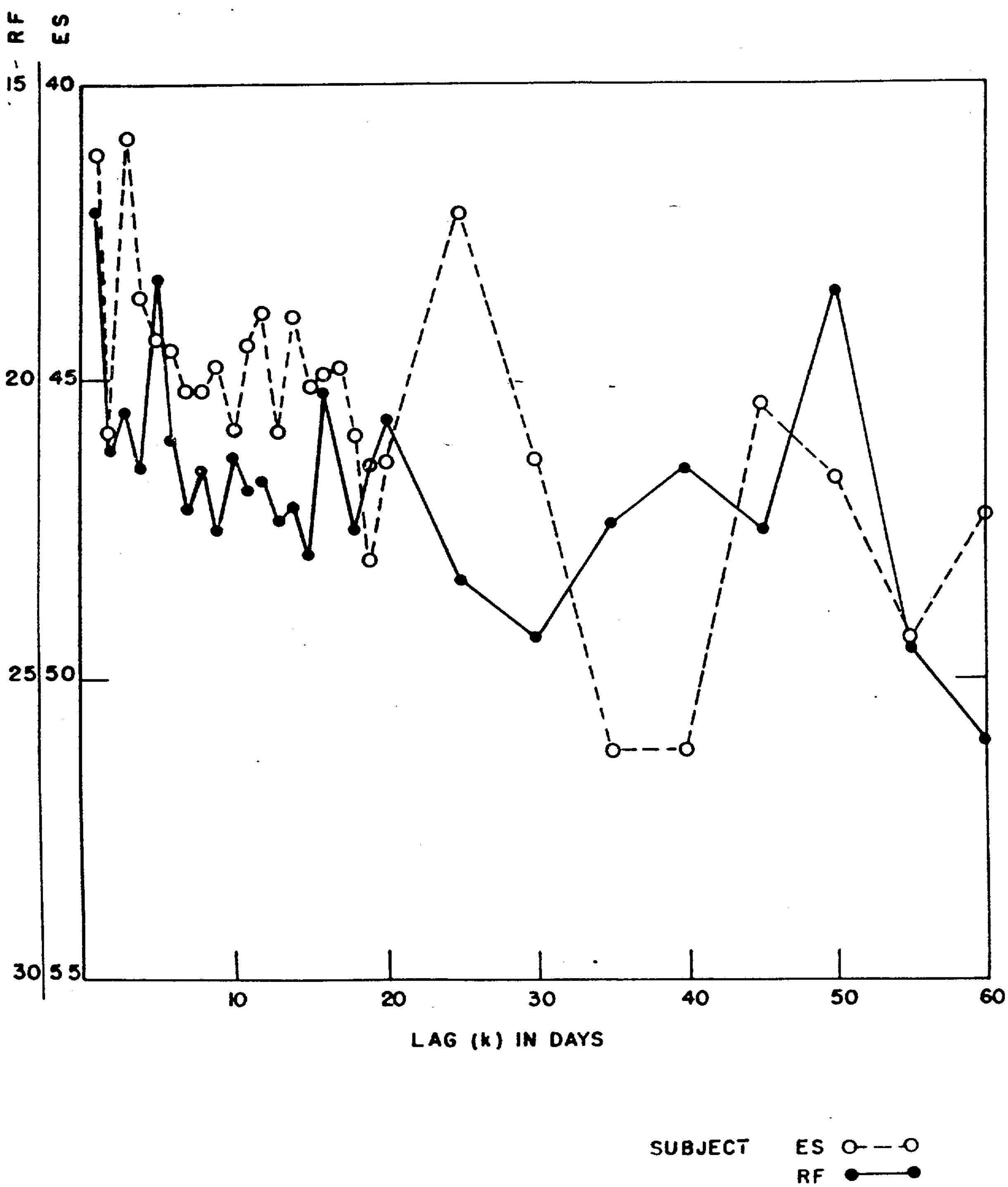
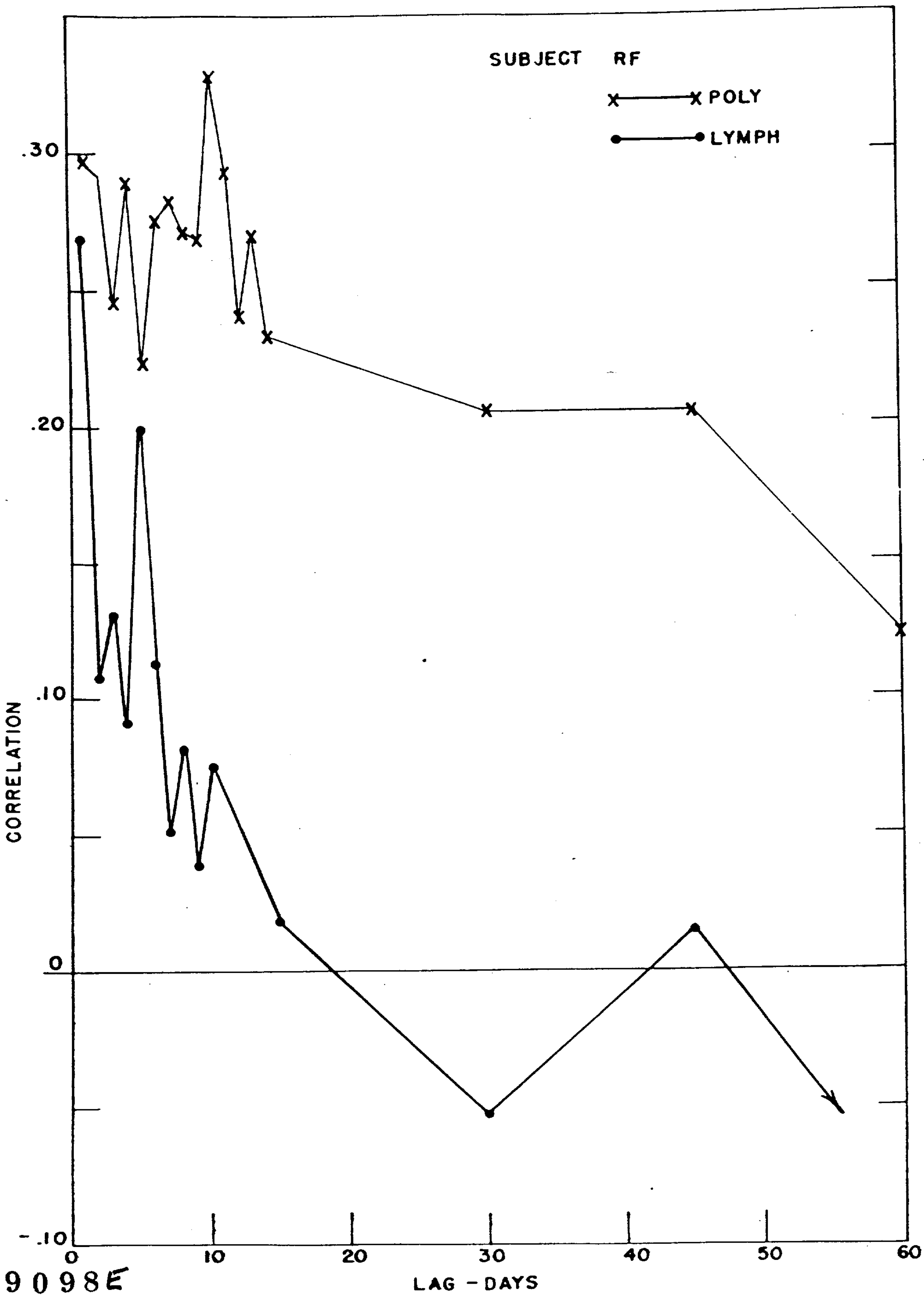


FIGURE 2

CORRELOGRAM FOR POLYS AND LYMPHS



one day in order to define the behavior of these systems more clearly. In addition to the long periods, there is evidence in the first 20 days of the existence of shorter periods.

The correlogram for the polymorphs of one subject (RF) are given in figure 2, with the correlogram for the lymphocytes of the same subject. In this figure the great difference in the statistical characteristics of the two systems may be clearly seen. The lymphocytes and polymorphs start off with correlations of about the same magnitude for a lag of one day, but thereafter the correlation for the lymphs drop off rapidly, while those for the polys decline slowly. The correlations for the lymphocytes drop below zero within 20 day lag, while those for the polys are still positive at 60 days lag and do not appear to reach zero level much before 90 days. This difference may be described by saying that the two systems have different relaxation times.

The behavior described above serves to indicate the difficulties in discussing the significance of differences between sets of measurements taken in succession on a single individual. While we are closing in on the solution, the answer will not be ready soon, and meanwhile the interpretation of several sets of data of this type must remain in doubt.

B. Analysis of blood picture of white male laboratory personnel. Single blood counts on 238 white male laboratory employes were analysed. The following variables were investigated:

1. logarithm of 60 minute sedimentation
2. hematocrit
3. red blood cell count
4. absolute polymorphonuclear count
5. absolute lymphocyte count
6. age

exposure hazard and nature of work were disregarded. The variable of particular interest was the sedimentation, so every subject is represented by a sedimentation measure. As many as 40 subjects did not have measures of one or more of the other variables, but for any pair of variables compared, the number of cases exceeded 200.

Product-moment correlations and correlation ratios were computed for the 15 distinct pairs of the six variables. Correlation coefficients are recorded in Table 2. The two highest intercorrelations are (a) sedimentation vs. age ($r_{16} = +0.478$) and (b) poly vs. lymph ($r_{45} = +0.333$). Correlations greater than +0.14 or less than -0.14 are significantly different from zero (5 per cent level). Thus 10 of the 15 combinations of variables show significant relationship. The results agree with previous results, for those relationships previously investigated.

A complete table of partial correlation coefficients of the fourth order was computed, and is reported in Table 3. The coefficients recorded here give the strength of the relationship between two variables when the remaining four variables are held constant. Thus, if X and y are positively correlated, but both are in addition positively correlated with z, the first-order partial correlative $r_{xy.z}$ will be smaller in magnitude than the zero order correlation r_{xy}.

It may be seen by comparing Tables 2 and 3 that for the most part there is little difference between the zero order and fourth order coefficients. Two of the fourth order coefficients are significantly different from their corresponding zero order coefficients. The correlation between sedimentation and lymphocyte count changed from zero ($r_{15} = -0.004$) to a significant negative value ($r_{15.2346} = -0.147$), and the correlation between polymorph count and age changed from a significant positive value ($r_{46} = +0.207$) to a non-significant value ($r_{46.1235} = +0.059$).

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Table 8

Zero order product moment correlations of the following variables:

1. logarithm of 60 minute sedimentation
2. hematocrit
3. red blood cell count
4. absolute polymorphonuclear leuocyte cell count
5. absolute lymphocyte cell count
6. age in years at time of count.

White male laboratory personnel.

	1	2	3	4	5	6
1						
2	-.155					
3	-.244	+.229				
4	+.245	+.168	-.032			
5	-.004	+.165	+.041	+.033		
6	+.478	+.038	-.255	+.207	+.077	

Table 3

Fourth order correlation coefficients for the same variables and population as in Table 1

	1	2	3	4	5	6
1						
2	-.204					
3	-.183	+.217				
4	+.244	+.158	-.006			
5	-.147	+.089	+.023	+.316		
6	+.423	+.142	.194	+.059	+.052	

When the effect of other variables is removed, the polymorph and lymphocyte counts are not significantly dependent on age. The net dependence of hematocrit and red count on age is interesting because the former comes out with a significant positive correlation while the latter has a significant negative correlation with age. Both have significant negative partial correlations with sedimentation.

The results indicate that several independent factors are necessary to account for the normal blood picture. More will be said about this later.

After-Survival of Mice Treated with Single Doses of X Rays. Figures 3-7 and their legends give a synopsis of the chronic survival of mice which received single X-ray doses while young. The mice were the survivors of the groups used by C.W. Hagen in establishing the acute survival curves. Two strains of mice are represented, namely, CF_1 females, and ABC mice of both sexes. The thirty-day LD_{50} for these strains was about 550 r, and the minimum lethal dose was about 300 r.

The analysis was conventional for the survivorship curves (Figures 3 and 4) and for the after-expectation curve (Figure 5). Figures 6 and 7 are essentially rate of mortality diagrams, but the method of computation, described briefly in the legend, is novel, and was employed because of the special problems which arise in computing rate of mortality statistics for small groups on relatively large intervals.

The general conclusion is that single doses of X rays have effects on the after-expectation of life which are comparable to the acute effects of these doses. For example, a dose (500 r) which causes 50 per cent killing within 30 days, reduces the after-expection of the survivors (Carworth females) by about 50 per cent, while 200 r, which causes no early killing, has no significant effect on the length of after-survival. This would indicate that the late mortality is related to the gravity of acute injury and consequent scar tissue formation, rather than to latent direct injury, since the expression of latent direct injury should be roughly proportional to the administered dose. Studies now under way are intended to answer some of the questions raised by this preliminary investigation.

Figure 3. Survivorship of CF_1 ♀ mice after single doses of X rays at about 8-12 weeks of age. Only those mice included which survived for at least 30 days after exposure.

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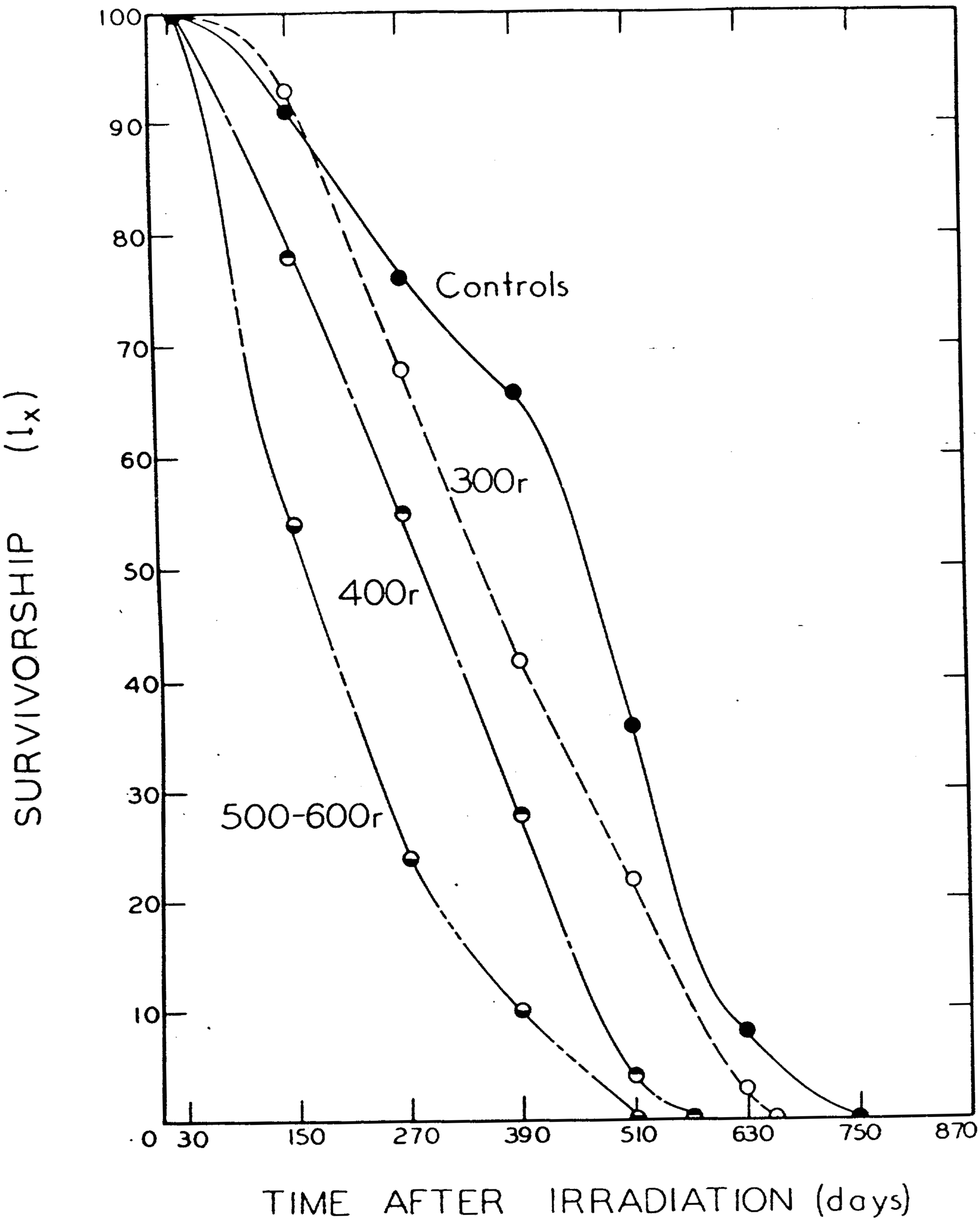

SURVIVORSHIP (1_x)
100
90
80
70
60
50
40
30
20
10
0
30
150
270
390
510
630
750
870
TIME AFTER IRRADIATION (days)
Controls
300r
400r
500-600r

Figure 4. Survivorship of ABC male and female mice after single doses of X rays at about 8-12 weeks of age. Only those mice included which survived at least 30 days after exposure. Dose levels combined because different dose groups kept in a single cage.

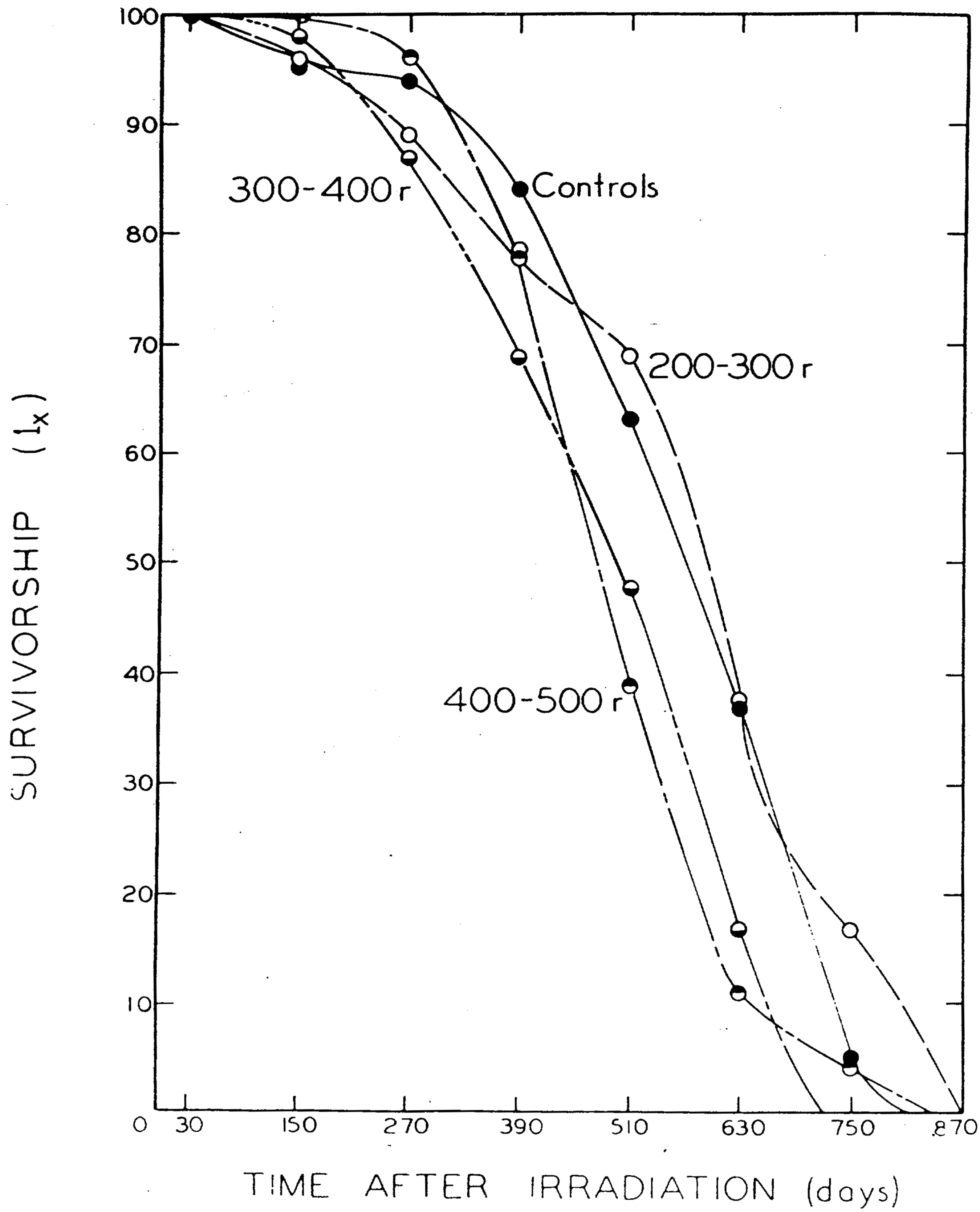
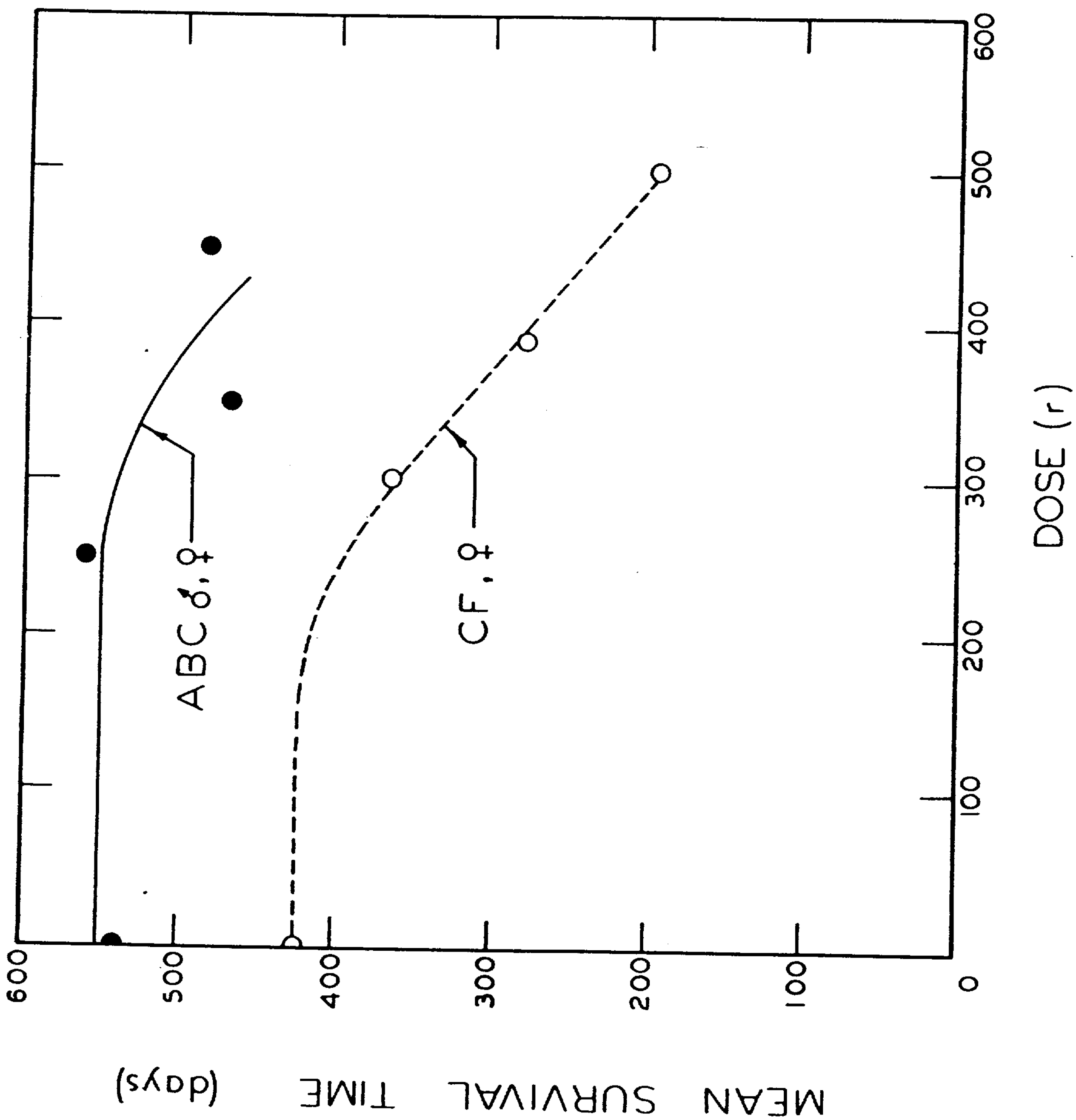

100
90
80
70
60
50
40
30
20
10
0
30
150
270
390
510
630
750
870
300-400 r
Controls
200-300 r
400-500 r
SURVIVORSHIP (l_x)
TIME AFTER IRRADIATION (days)

Figure 5. Mean after-survival of mice exposed to single doses of X rays at 8 - 12 weeks of age. Same groups as for figures 3 and 4. Note rapid decrease as doses enter the range of fractional acute lethality. Note also that slope of the rapidly decreasing portion and "threshold" dose are of a sameness for the two strains.



MEAN SURVIVAL TIME (days)
600
500
400
300
200
100
0
DOSE (r)
100
200
300
400
500
600
ABC ♂, ♀
CF, ♀

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Figure 6. Logarithm of instantaneous rate of mortality plotted against time after treatment, for CF_1 females. Scale of conventional death rates on right hand side. Note straight-line form and approximate constancy of slopes for the four groups. The points plotted are the values:

$$-\Delta \log l_x$$

on a log scale, so that the straight line relation may be written

$$\log(-\Delta \log l_x) = At + B$$

The differencing interval was 120 days, beginning 30 days after treatment. Conventional death rate

$$q_x = \frac{l_x - l_{x+h}}{l_x},$$

is an approximation to the expression above, but is not satsifactory for q_x approaching unity.

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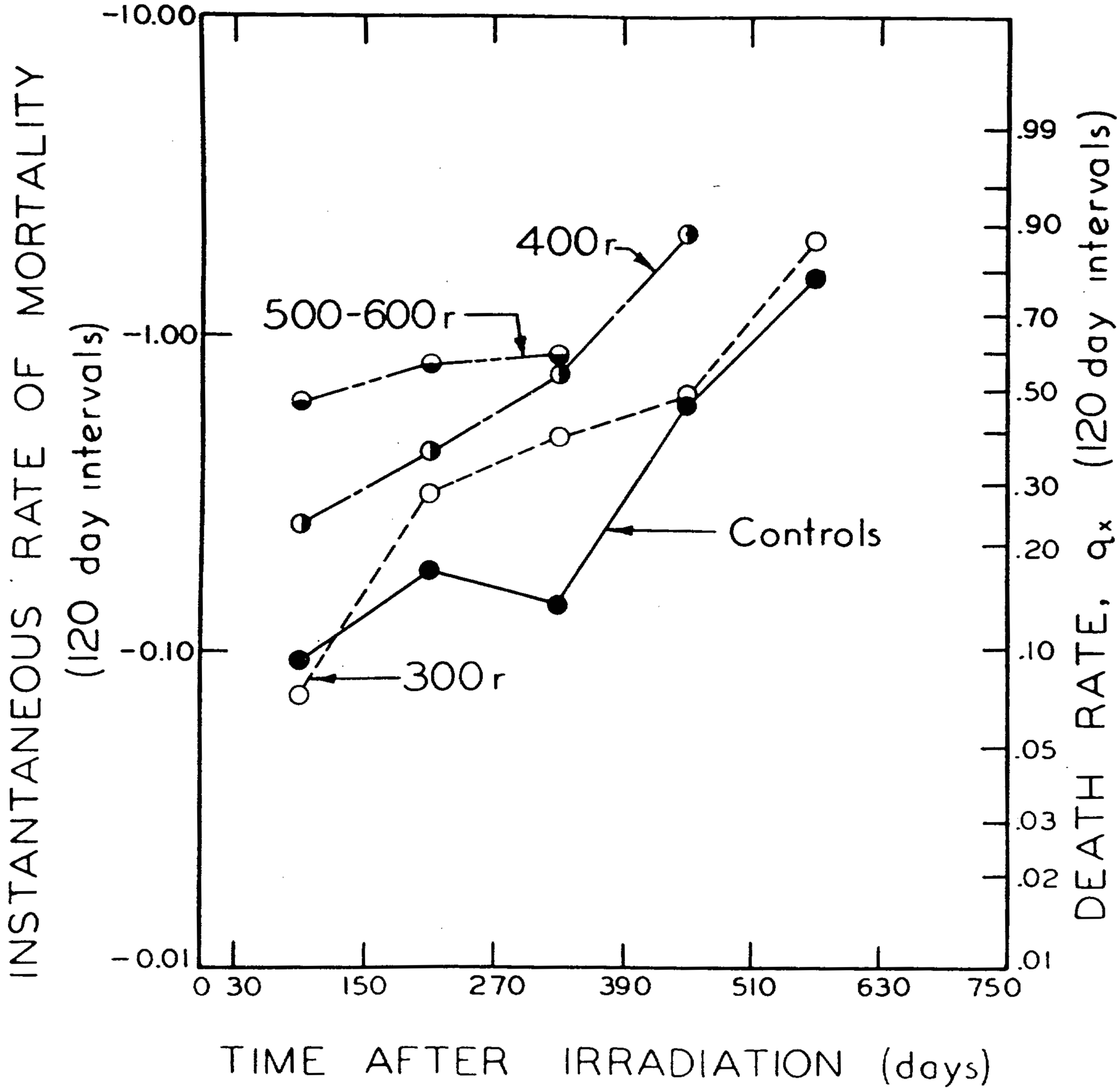
-10.00
-1.00
-0.10
-0.01
.99
.90
.70
.50
.30
.20
.10
.05
.03
.02
.01
0 30
150
270
390
510
630
750
400 r
500-600 r
Controls
300 r
INSTANTANEOUS RATE OF MORTALITY
(120 day intervals)
DEATH RATE, q_x (120 day intervals)
TIME AFTER IRRADIATION (days)

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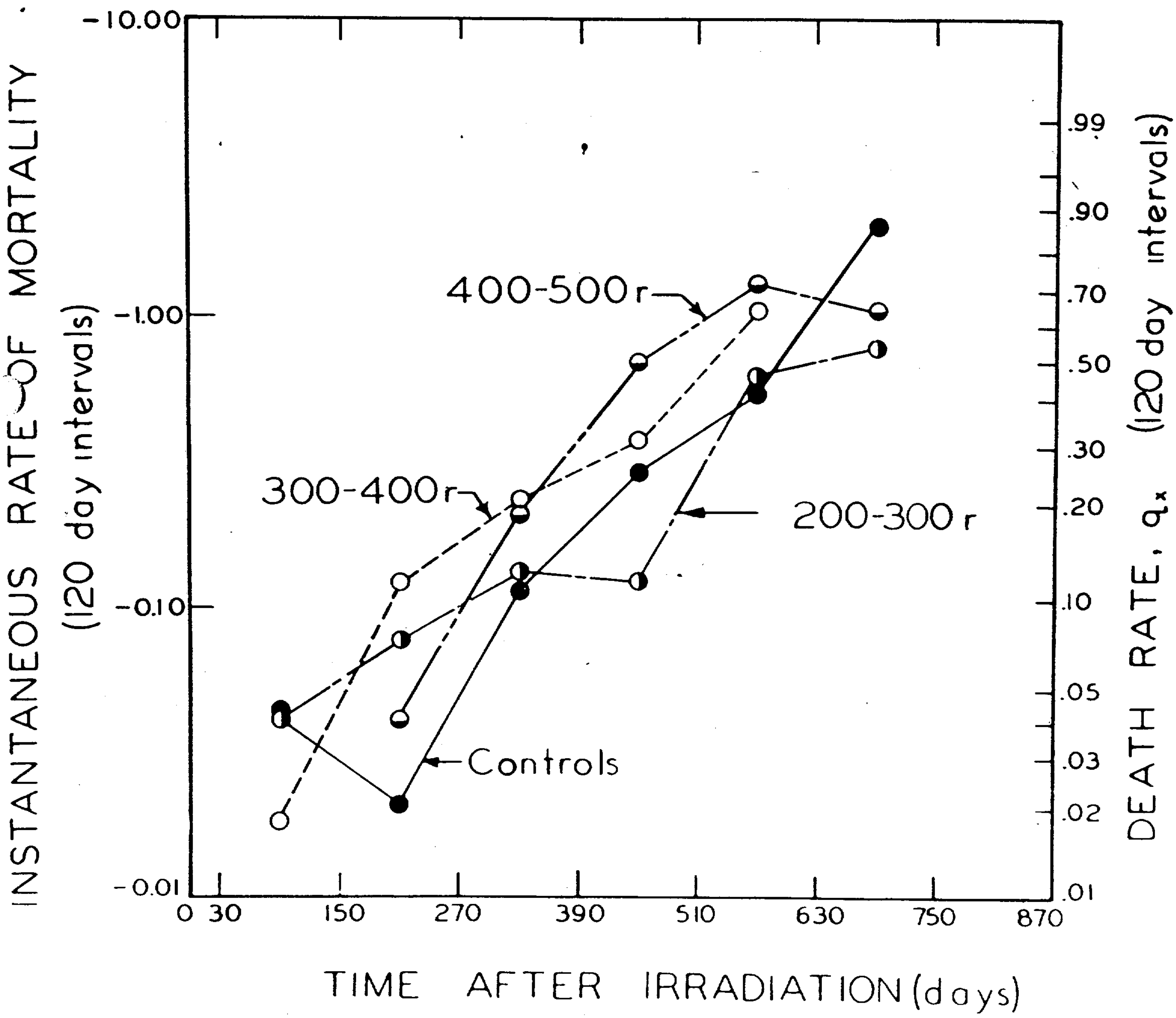

INSTANTANEOUS RATE OF MORTALITY (120 day intervals)
-10.00
-1.00
-0.10
-0.01
DEATH RATE, q_x (120 day intervals)
.99
.90
.70
.50
.30
.20
.10
.05
.03
.02
.01
400-500 r
300-400 r
200-300 r
Controls
0 30 150 270 390 510 630 750 870
TIME AFTER IRRADIATION (days)