Dose-Response Relationship of Neutron and Gamma Rays to Chromosomally Aberrant Cells among Atomic Bomb Survivors in Hiroshima and Nagasaki

MASANORI OTAKE

Department of Epidemiology and Statistics
Radiation Effects Research Foundation, Hiroshima, Japan
and
Faculty of Integrated Arts and Sciences
Hiroshima University, Hiroshima, Japan
(Received July 4, 1979)

Chromosome/Dose-Response/RBE

The quantitative relationship of the frequency of cells with radiation-induced chromosome aberrations in peripheral leukocytes in atomic bomb survivors has been evaluated as a function of gamma and neutron doses. Three different models have been examined; each assumes a linear or a non-linear response to gamma rays and a linear-response to neutrons. From the standpoint of the goodness of fit of these models, the model which "best" fits the data on the frequency of cells with radiation-induced chromosome aberrations is the exponent model, where the frequency of aberrant cells increases exponentially with dose.

The goodness of fit for this model shows the frequencies of cells with any chromosome aberration or an exchange aberration to be dependent cubically on the gamma ray dose and linearly on the neutron dose. The result derived from the frequency of aberrant cells gives a conservative dose-response relationship. The relative biological effectiveness (RBE) of neutrons for frequency of cells with any chromosome aberration is calculated to be 13 at 30 rad of neutrons, 6 at 100 rad, 3 at 300 rad and so on.

INTRODUCTION

The development of structural abnormalities in chromosomes following exposure to ionizing radiation has been repeatedly shown in experiments using animals and plants, and numerous studies document the types and frequencies of radiation-induced chromosome aberrations\(^{1-8}\). Studies of atomic bomb survivors have revealed that aberrations are not only induced by ionizing radiation in the chromosomes of human peripheral leukocytes, but that they continue to exist for many years after radiation exposure even in persons who are clinically normal\(^{4-9}\). Awa et al.\(^{5}\) found a difference between Hiroshima and Nagasaki in the dose-response of radiation-induced chromosome aberrations in atomic bomb survivors and reported that the frequency of chromosome aberrations, which increases with dose, is consistently higher in Hiroshima than in...
Nagasaki. This difference in dose response may be due to the difference in the neutron-versus-gamma composition between the two atomic bombs. There is as yet, however, no paper which clarifies the relationship between the frequency of radiation-induced chromosomally aberrant cells and the dose in gamma rays and neutrons.

The purpose of this paper is, first, to determine the dose-response relationship of gamma rays and neutrons to the frequency of cells with chromosome aberrations in atomic bomb survivors, and, second, to estimate the RBE of neutrons with respect to chromosome aberrations.

**MATERIAL**

The subjects of this investigation were selected from the Adult Health Study (AHS) sample\(^4,16\), on whom detailed clinical examinations are conducted biennially by the Radiation Effects Research Foundation (RERF), based on dose groups stratified according to tentative dose estimates\(^11\). All atomic bomb survivors exposed to 100

| Total dose (rad) | Mean dose (rad) | Number of cases | Number of cells observed | Any aberration | Exchange aberration |
|------------------|-----------------|-----------------|--------------------------|----------------|---------------------|
|                  |                 |                 |                          | Number of cells | %                  | Number of cells | %                  |
| **Hiroshima**    |                 |                 |                          |                |                    |                |                    |
| Control          | 0               | 263             | 24414                    | 294            | 1.20                | 210             | .86                |
| 1-69             | 28.88           | 58              | 5259                     | 102            | 1.94                | 76              | 1.45                |
| 70-139           | 112.63          | 82              | 7613                     | 354            | 4.65                | 300             | 3.94                |
| 140-209          | 173.07          | 77              | 7151                     | 436            | 6.10                | 375             | 5.24                |
| 210-299          | 249.32          | 62              | 5554                     | 524            | 9.43                | 462             | 8.32                |
| 300-399          | 348.44          | 43              | 3896                     | 489            | 12.55               | 433             | 11.11               |
| 400-499          | 441.13          | 30              | 2869                     | 407            | 14.19               | 371             | 12.93               |
| 500-999          | 665.56          | 25              | 2413                     | 471            | 19.52               | 436             | 18.07               |
| 1000+            | 2165.22         | 9               | 809                      | 61             | 7.54                | 53              | 6.55                |
| Total            | —               | 649             | 59978                    | 3138           | 5.23                | 2716            | 4.53                |
| **Nagasaki**     |                 |                 |                          |                |                    |                |                    |
| Control          | 0               | 156             | 14748                    | 199            | 1.35                | 128             | .87                |
| 1-69             | 32.43           | 40              | 3887                     | 63             | 1.62                | 49              | 1.26                |
| 70-139           | 106.47          | 44              | 4676                     | 69             | 1.69                | 52              | 1.28                |
| 140-209          | 170.43          | 37              | 3383                     | 68             | 2.01                | 49              | 1.45                |
| 210-299          | 251.54          | 56              | 5296                     | 149            | 2.81                | 117             | 2.21                |
| 300-399          | 336.10          | 30              | 2753                     | 94             | 3.41                | 83              | 3.01                |
| 400-499          | 437.17          | 24              | 2312                     | 164            | 7.09                | 147             | 6.36                |
| 500-999          | 649.75          | 12              | 1166                     | 147            | 12.61               | 140             | 12.01               |
| 1000+            | 1112.25         | 4               | 400                      | 59             | 14.75               | 56              | 14.00               |
| Total            | —               | 403             | 38021                    | 1012           | 2.66                | 821             | 2.16                |
rad or more who visited the former Atomic Bomb Casualty Commission (ABCC) for periodic examination from 8 January 1968 to 17 December 1970 in Hiroshima and from 5 January 1968 to 3 March 1971 in Nagasaki were selected and, as a comparison group, subjects on the daily schedule of the AHS sample at a ratio of one to one.

Of the 1,374 subjects selected during this study period (902 in Hiroshima and 472 in Nagasaki), 322 were excluded from the chromosome study because they had received fluoroscopy, radiotherapy or radioisotope irradiation or because the culture was unsuccessful or less than 30 scorable cells could be identified. Consequently, 649 subjects in Hiroshima and 403 subjects in Nagasaki were used (Table 1). The culture time was 52 hours including the last two hours of colchicine treatment, so that most of the observed metaphases appeared to be in their first in vitro cell division. The details regarding the material and the methods have been reported previously6,8.

STATISTICAL CONSIDERATIONS AND METHODS

The extent of the biological effects resulting from increased radiation is determined primarily by the quantitative relationship of dose and its effect. Many different relationships can be envisaged. These include situations in which the effects increase linearly, quadratically, exponentially or logistically with dose.

The first critical evaluation of radiation-induced chromosome aberrations appears to be that of Sax15 who examined the effect of X-irradiation on the microspore chromosome of the plant Tradescantia. He found a good fit using the equation $Y = D^k$ where $Y$ is the yield in dicentric and ring chromosome aberrations and $D$ is the X-ray dose. This relationship can, of course, be expressed more generally as $Y = \alpha + \beta D^k$ or $Y = \alpha + \beta D^k$, where $k$ denotes the number of effective hits, $\alpha$ the yield in aberrations observed in the nonirradiated control cells, and $\beta$ a constant13,14.

In the evaluation of radiation-induced changes in atomic bomb survivors special attention must be given to the fact that the survivors were exposed simultaneously to both gamma rays and neutrons. Moreover, the dose-response relationship must take into account the large difference in output of gamma rays and neutrons between the Hiroshima bomb (a uranium one) and the Nagasaki bomb (a plutonium one).

Recently, Otake15 and Ishimura et al.16 in a study of leukemia examined the dose-response relationship for the frequency of leukemia ($P$) using a model based on gamma rays ($D\gamma$) and neutrons ($D\eta$). The general equation they used can be expressed as $P_{ij} = \alpha_i + \beta_1 D\gamma_{ij} + \beta_2 D\eta_{ij}$ ($i=1, \ldots, c$; $j=1, \ldots, m$), where $\alpha_i$ is the frequency of the event in the nonexposed control group in the $i$-th category; $D\gamma_{ij}$ and $D\eta_{ij}$ are the mean gamma dose and mean neutron dose of the $(i, j)$ th cell; and $\beta_1$ and $\beta_2$ are the constants expressing the dose-response common to the $c$ categories. They evaluated the goodness of fit of this model when $k=1$ and $k=2$, that is, for a "linear" and "quadratic dependence" on gamma rays. This method, a technique generally similar to that of the dose-response curve introduced in the UN report10 and by Evans10, gave a good fit to the leukemia incidence data.
The relation between survival rate \((1-P)\) and dose \((D)\) introduced by Lea\(^5\) in 1955 assumes an exponential linear decrease of the form, \((1-P)=\exp(-\beta D)\), where \(P\) is the mortality rate and \(\beta\) a constant of radiosensitivity. If the frequency of cells with radiation-induced chromosome aberrations is \(P\), this equation can be expanded into \(P=1-\exp(-\alpha-\beta_1D_{\gamma}^k-\beta_2D_{n})\) which has been called the exponit model\(^6\). If some "dampening" of the effect of exposure at higher doses exists as could arise if differential cell selection occurs, a logistic response model might be appropriate, that is,

\[
P=1/[1+\exp(-\alpha-\beta_1\gamma_{ij}^k-\beta_2D_{nij})].
\]

In order to examine the gamma and neutron components in the dose-response relationship, the frequency of chromosomally aberrant cells \((P_{ij})\) was evaluated with each of the models:

Model I: \(P_{ij}=\alpha_i+\beta_1D_{\gamma ij}+\beta_2D_{nij}\)

Model II: \(P_{ij}=1-\exp(-\alpha_i-\beta_1D_{\gamma ij}^k-\beta_2D_{nij})\)

Model III: \(P_{ij}=1/[1+\exp(-\alpha_i-\beta_1\gamma_{ij}^k-\beta_2D_{nij})]\).

Here, the subscript \(i=1, 2\) designates Hiroshima or Nagasaki, subscripts \(j\) the dose classifications, \(k\) the extrapolation number of the gamma ray dose, and \(D_{\gamma ij}\) and \(D_{nij}\) the mean gamma and mean neutron doses to the \((i, j)\) th cell, respectively. The details of the statistical procedures are described in Appendix 1.

**EVALUATION OF CHROMOSOME DATA**

Awa et al.\(^5\) reported from a study of the effect of age on chromosome aberrations that although there seems to be a tendency for the frequency of aberrant cells in the high age group of the control population to be slightly higher than that in the low age group in both cities, no statistically significant difference was observed. However, much variation in the frequency of cells with chromosome aberrations is observed in the relationship between age and dose because the number of cases is so small (Table 2). A conservative approach under these circumstances is to assume the cities are different and to fit a separate constant to each. This we have done.

Figures 1 and 2 show by 10-rad intervals of total dose the frequency distribution of cells with one or more chromosome aberrations per individual in Hiroshima and Nagasaki. As is evident from the figures for the two cities, large variation in the frequency of cells with chromosome aberrations occurs with increase in dose. We believe these differences\(^5\) between individuals to be attributable to their statuses of health, complicated breakage due to the random nature of the radiation effects, and possibly errors in the estimation of their exposure.

It seems proper to evaluate the average risks of aberrant cells for appropriate dose groups as a function of the mean gamma and mean neutron doses for those groups, but the choice of the dose intervals is a difficult one. There are no generally
Table 2
Distribution of aberrant cells in Hiroshima and Nagasaki by age and dose

| Total dose (rad) | <30 Age ATB* | ≥30 Age ATB* |
|-----------------|--------------|--------------|
|                 | Number of cases | Number of cells observed | Number of cells | % | Number of cases | Number of cells observed | Number of cells | % | Number of cells | % |
| Control         | 120 | 10971 | 118 | 1.08 | 85 | .77 | 143 | 13443 | 176 | 1.31 | 125 | .93 |
| 1-69            | 25  | 2171 | 32  | 1.47 | 23 | 1.06 | 33  | 3088 | 70  | 2.27 | 53  | 1.72 |
| 70-139          | 35  | 3340 | 140 | 4.19 | 122 | 3.65 | 47  | 4273 | 214 | 5.01 | 178 | 4.17 |
| 140-209         | 29  | 2752 | 168 | 6.10 | 145 | 5.27 | 48  | 4399 | 268 | 6.09 | 230 | 5.23 |
| 210-299         | 37  | 3242 | 296 | 9.13 | 256 | 7.90 | 25  | 2312 | 228 | 9.86 | 206 | 8.91 |
| 300-399         | 28  | 2509 | 319 | 12.71| 280 | 11.16| 15  | 1387 | 170 | 12.26| 153 | 11.03|
| 400-499         | 18  | 1749 | 259 | 14.81| 237 | 13.55| 12  | 1120 | 148 | 13.21| 134 | 11.96|
| 500-999         | 11  | 1013 | 210 | 20.73| 198 | 19.55| 14  | 1400 | 261 | 18.64| 238 | 17.00|
| Total           | 303 | 27747| 1542| 5.56 | 1346| 4.85 | 337 | 31422| 1535| 4.89 | 1317| 4.19|

Hiroshima

Nagasaki

* Age ATB denotes age at the time of bombing.
Fig. 1. Frequency distribution of cells with any aberration per case by dose group at 10 rad intervals in Hiroshima.

Fig. 2. Frequency distribution of cells with any aberration per case by dose group at 10 rad intervals in Nagasaki.
accepted statistical conventions on how to establish the optimal dose intervals for chromosome data. It seems reasonable, however, to classify the data on the basis of intervals of equal widths and this we have done. The frequency of aberrant cells based upon intervals of equal widths\(^2\) i.e., 0, 1-99, \(\ldots\), 400-499, 500+, has been evaluated for each of three regression models. The fit of any one of these models is very poor. As is evident from Table 1 in Awa et al.\(^6\) and Figures 1 and 2, the number of A-bomb survivors decreases with increasing dose. The frequency of aberrant cells seems to vary widely with dose, but the data are not extensive. To improve the fit we chose dose intervals so as to present as smooth a curve as practicable based upon the frequency of aberrant cells in the two cities and the sample size in each dose interval. However, we were unable to use intervals of equal widths throughout the dose range because the sample sizes became too small. The data on the 1000 rad and over group differ markedly from adjacent dose intervals in both cities. A large error\(^1\) may exist, however, in the estimation of the tentative doses for the 1000 rad and over groups in the two cities; we have, therefore, excluded the

### Table 3

Distribution of aberrant cells by city and dose applied to dose-response relationship of chromosome data

| Total dose (rad) | Mean dose (rad) | Number of cells observed | Any aberration | Exchange aberration |
|----------------|----------------|--------------------------|----------------|---------------------|
|                | Gamma | Neutron | Number of cells observed | Number of cells | % | Number of cells | % |
| **Hiroshima** |       |         |                           |                |   |                   |   |
| Control        | 0     | 0       | 24414                     | 294            | 1.20 | 210              | 0.86 |
| 1-69           | 23.29 | 5.59    | 5259                      | 102            | 1.94 | 76               | 0.45 |
| 70-139         | 87.72 | 24.91   | 7613                      | 354            | 4.65 | 300              | 3.94 |
| 140-209        | 135.01 | 38.06  | 7151                      | 436            | 6.10 | 375              | 5.24 |
| 210-299        | 191.92 | 57.40  | 5554                      | 524            | 9.43 | 462              | 8.32 |
| 300-499        | 291.76 | 94.77  | 6765                      | 896            | 13.24 | 804              | 11.88 |
| 500-600        | 399.17* | 142.94* | 2413                      | 471            | 19.52 | 436              | 18.07 |
| Total          | ------ | ------- | 59169                     | 3077           | 5.20 | 2663             | 4.50 |

| **Nagasaki** |       |         |                           |                |   |                   |   |
| Control       | 0     | 0       | 14748                     | 199            | 1.35 | 128              | 0.87 |
| 1-69          | 32.40 | .03     | 3887                      | 63             | 1.62 | 49               | 1.26 |
| 70-139        | 106.02 | .45    | 4076                      | 69             | 1.69 | 52               | 1.28 |
| 140-209       | 168.24 | 2.19   | 3383                      | 68             | 2.01 | 49               | 1.45 |
| 210-299       | 247.51 | 3.93   | 5296                      | 149            | 2.81 | 117              | 2.21 |
| 300-499       | 374.65 | 6.37   | 50685                     | 258            | 5.09 | 230              | 4.54 |
| 500-600       | 531.59* | 12.63* | 1166                      | 147            | 12.61 | 140              | 12.01 |
| Total         | ------ | ------- | 37621                     | 953            | 2.53 | 765              | 2.03 |

\(\ast\) Mean gamma and mean neutron doses in the 500-600 rad group were obtained by arbitrarily setting the dose received by survivors having dose estimates of more than 600 rad at 600 rad.
13 cases with purported exposures of 1000 rad or more from the analysis. As is shown in Table 3, the frequency distribution of chromosome aberrations by city and dose is employed in evaluating the dose-response in this study.

RESULTS

Determination of the "Best" Model and Dose-Response Relationship

The respective chi-square values for each extrapolation number of the gamma rays ($k=1, 2, \cdots, 5$) for each model and the goodness of fit of these models are shown by type of chromosome aberrations in Table 4. The logistic model (Model III) gives a very poor fit to the data generally and Model I shows a poor fit to the frequency of all aberrant cells with exchange aberrations. Only the exponent model (Model II) shows a good fit to the chromosome data.

Table 4

| Type of aberrations | $x^2$ value by extrapolation number (k) |
|---------------------|----------------------------------------|
|                     | 1       | 2       | 3       | 4       | 5       |
| Model I: $P_{ij} = \alpha_i + \beta_i D_{\gamma i} + \beta_i D_{\nu i}$ |
| Any                 | 88.66***| 35.10***| 24.15** | 26.98** | 37.72***|
| Exchange            | 105.32***| 39.26***| 23.32** | 25.08** | 37.23***|
| Model II: $P_{ij} = 1 - \exp(-\alpha_i - \beta_i D_{\gamma i} - \beta_i D_{\nu i})$ |
| Any                 | 90.65***| 29.33** | 14.48N.S.| 15.80N.S.| 25.90** |
| Exchange            | 109.76***| 36.29***| 16.63N.S.| 16.62N.S.| 27.69** |
| Model III: $\log[P_{ij}/(1-P_{ij})] = \alpha_i + \beta_i D_{\gamma i} + \beta_i D_{\nu i}$ |
| Any                 | 268.94***| 503.62***| 568.41***| 581.59***| 580.68***|
| Exchange            | 266.07***| 532.95***| 608.21***| 626.14***| 628.34***|

The superscripts for the $x^2$ values with 10 degrees of freedom express the following levels of significance:
N.S.: $P>0.05$, **: $P<0.01$, ***: $P<0.001$

Using Model II, the dose-response relationship of the frequency of cells with radiation-induced chromosome aberrations was determined by the goodness of fit of the model to the data. The best fit occurs with $k=3.4$ ($x^2=13.64$ for 10 d.f., $p>0.10$ N.S.) for the frequency of all aberrant cells and with $k=3.5$ ($x^2=14.88$ for 10 d.f., $p>0.10$ N.S.) for the frequency of exchange aberrant cells. Thus, the dose-response of chromosome aberrations can be considered to be dependent cubically on the gamma ray dose and linearly on the neutron dose. A very high and significant dose-response for the frequency of cells with chromosome aberrations was noted between gamma rays and neutrons (Table 5).
Table 5
Dose-response relationship of regression coefficients estimated from Model II with k=3

| Item                  | Estimated regression coefficients |  
|-----------------------|-----------------------------------|
|                      | $\hat{\alpha}_U$ (Hiroshima)     |
|                      | $\hat{\alpha}_N$ (Nagasaki)      |
|                      | $\hat{\beta}_1$                  |
|                      | $\hat{\beta}_2$                  |
| **Any aberration**   |                                   |
| Estimate             | .012459                           |
|                      | .014426                           |
|                      | .059858 × 10^{-8}***             |
|                      | .001276***                       |
| Standard error       | .067340 × 10^{-2}                |
|                      | .074481 × 10^{-2}                |
|                      | .046546 × 10^{-9}               |
|                      | .035659 × 10^{-2}                |
| Covariance           |                                   |
|                      | Cov (\hat{\beta}_1, \hat{\beta}_2) = -.059430 × 10^{-14} |
| **Exchange aberration** |                                   |
| Estimate             | .008791                           |
|                      | .009724                           |
|                      | .059163 × 10^{-8}***             |
|                      | .001147***                       |
| Standard error       | .056848 × 10^{-2}                |
|                      | .061963 × 10^{-2}                |
|                      | .043775 × 10^{-9}               |
|                      | .032952 × 10^{-2}                |
| Covariance           |                                   |
|                      | Cov (\hat{\beta}_1, \hat{\beta}_2) = -.051716 × 10^{-14} |

*** denotes significance of regression coefficients with $P < .001$

 Relative Biological Effectiveness of Neutrons

The RBE of neutrons in relation to gamma rays is defined as the ratio of $X$- or gamma rays ($D_Y$) to neutrons ($D_n$), $D_Y/D_n$, in absorbed dose that produces the same prescribed biological effect in tissue. Therefore, the relationship $\beta_1 D_Y^2 = \beta_2 D_n$ can be readily obtained from Model II. Thus, an estimated RBE can be expressed as

$$RBE = \left( \frac{\hat{\beta}_2}{\hat{\beta}_1} \right)^{1/2} \left( \frac{1}{D_n} \right)^{2/3}$$

The RBE was calculated to be 128.7^{2/3} for the frequency of all aberrant cells and 124.6^{2/3} for exchange aberrant cells using the regression coefficients given in Table 5. The RBE values associated with any chromosome aberration were found to be 13.3 at 30 rad of neutrons, 6.0 at 100 rad, 2.8 at 300 rad and so on. The calculation of the 95% confidence intervals is described in Appendix 2.

DISCUSSION

**Dose-Response Relationship**

The close relationship to dose of the yield of radiation-induced chromosome aberrations has been demonstrated in vitro and in vivo by many investigators. In particular, recent studies using human and other mammalian cells have reported that the dose-response curve of the yield of chromosome aberrations is linear to neutrons and fits closely the square of gamma or X-rays, especially with regard to the most readily identifiable dicentrics and rings. Further, the relationship between chromosome aberrations or carcinogenesis and the dose of a single radiation, i.e., the dose-response relationship to X-rays or gamma rays, is that of an almost linear-quadratic dose-response curve.

Goodness of fit of the model is here used as the means of determining the dose-
response relationship of the frequency of chromosomally aberrant cells induced by atomic bomb radiation. Overall, as we have shown, the exponent model provides a particularly good fit, but this dose-response relationship is the same as that which describes the loss of activity of enzymes and DNA and the death of viruses and some types of bacilli, and differs somewhat from the multi-target theory or the multistage models of Atwood et al., Armitage et al., and Lee. Armitage and Doll observed that in humans the age-specific incidence rate of many types of cancers is proportional to a power of age and argued that this result would be expected under a multistage model. Lee also concluded that a mathematical model assuming the occurrence of some types of cancer by a multistage process gave a good fit to observed data.

Our model postulates that the frequency of cells with aberrations in city (i) and dose group (j) is \( (1 - e^{-kij}) \) where \( \lambda_{ij} = \alpha_i + \beta_j + \gamma_{ij} \). Although the frequency of aberrant cells increases exponentially with increasing radiation, a characteristic of this dose-response relationship is a linear dependence on neutron dose but a linear one or a curvilinear one on gamma exposure. Judging from the trend in frequency of cells with any chromosome aberration, it would seem that the dose-response relationship may differ somewhat between Hiroshima and Nagasaki. The expected frequency of aberrant cells in Hiroshima rises more or less linearly to about 200 rads,

![Fig. 3. Dose-response pattern with 95% confidence intervals of any chromosome aberration in Hiroshima and Nagasaki.](image-url)
and then somewhat more steeply beyond this dose. The expected frequency of aberrant cells in Nagasaki, on the other hand, is almost flat to 150 rad, with no evident risk of aberrations being induced by radiation, but rises curvilinearly in the range of 150 rad and over (Figure 3).

**Biological Significance**

Comparison of the frequency of all aberrant cells in Hiroshima and Nagasaki shows hardly any elevation of risk up to about 150 rad in Nagasaki where the neutron component is no more than 2 rad. In Hiroshima the neutron component in this dose range is about 30 rad. The observed average frequency of all aberrant cells induced in this dose range is about 3 times higher in Hiroshima than in Nagasaki. 

Awa et al. give the number of aberrations per aberrant cell by dose on data in Hiroshima only, i.e. 1.08 for control, 1.15 for 1-99 rad, 1.13 for 100-199 rad, 1.19 for 200-299 rad, 1.28 for 300-399 rad, 1.26 for 400-499 rad and 1.38 for 500+ rad. Consequently, the result derived from the frequency of aberrant cells gives a conservative dose-response relationship or underestimate of parameters on the effects of gamma and neutron doses because the number of aberrations per aberrant cell in the 500 rad and over group is about 1.3 times higher than that in the control group. In any case, chromosomal interchange and chromosomal intrachange occur at a high frequency with increasing dose, but some symmetric exchanges may result in no change in chromosome form and may not be observable grossly. Approximately 80 percent of radiation-induced chromosome aberrations by Awa et al. is occupied by reciprocal translocations and pericentric inversions. Such aberrations must be a mixture derived from long-lived lymphocytes and those that were due to transmission via the stem cells. The finding of a cubic effect for gamma rays and a linear effect for neutrons may be the result of the mechanism of induction and some selection due to repopulation divisions. The relative effects of the two will be influenced by the production of cells still in their first cell cycle after irradiation and those which have been derived from irradiated stem cells. According to a recent research report, a significant relationship has been found between radiation and carcinogenesis. However, the relationship between chromosome aberrations in peripheral lymphocytes and carcinogenesis has not been clarified yet. The repair mechanism(s) of cells is also largely unknown at present.

**Evaluation of RBE**

Numerous studies have been published on the RBE of different forms of ionizing radiation (see, for example). In 1970 Rossi, for example comparing a number of neutron energies against X-rays, reported that the RBE value for opacification of the murine lens was $44/\sqrt{Dn}$, where $Dn$ is neutron dose. He and Kellerer subsequently summarized in one figure the RBE findings of many investigators.

In a study of leukemia in atomic bomb survivors, Otake reviewed 6 different simple models, all functions of gamma and neutron doses, and sought the RBE value.
for those models in which the estimated values of the parameters were all positive. He reported that the RBE value was $40.3/\sqrt{Dn}$ when he used leukemia mortality data. Ishimaru et al. estimated the RBE values for Kerma and marrow dose using leukemia incidence data and reported a value of $45.0/\sqrt{Dn}$ for the former and a value of $48.4/\sqrt{Dn}$ for the latter. Scott et al. pointed out that the RBE value varies from 3.3 with a 37.4 neutron dose to 2.6 with a 157.4 neutron dose for dicentric plus rings per cell. Biola et al. investigated in vitro the dose-response relationship for different doses, i.e., neutron and gamma, of dicentric chromosomes in human lymphocytes. They reported that the RBE values for neutron doses of 5.7, 57.5, 115, and 172 rad were 13.2, 5.7, 3.9, and 3.4 respectively. From Model II, values of RBE with 95% confidence intervals (Appendix 2) were obtained for the frequency of cells with any or merely exchange aberration. The results are shown in the table below:

| Extrapolation number | Neutron dose in rad | Any aberration | Exchange aberration |
|----------------------|---------------------|----------------|---------------------|
|                      | 1                   | 50            | 100                | 200                | 300                |
| $k=3.0$              |                     |               |                    |                    |
| RBE                  | 128.7               | 9.5           | 6.0                | 3.8                | 2.9                |
| 95% Upper            | 136.6               | 10.1          | 6.3                | 4.0                | 3.1                |
| Lower                | 121.2               | 8.9           | 5.6                | 3.5                | 2.7                |
| $k=3.0$              |                     |               |                    |                    |
| RBE                  | 124.6               | 9.2           | 5.8                | 3.6                | 2.8                |
| 95% Upper            | 132.1               | 9.7           | 6.1                | 3.9                | 3.0                |
| Lower                | 117.7               | 8.7           | 5.5                | 3.4                | 2.6                |

Note: The upper and lower confidence limits of RBE estimate are not symmetrical rounds.

It is of interest from the radiobiological viewpoint that, whereas the RBE for any chromosome aberration appears higher than the RBE for leukemia in the low dose range, a tendency is suggested for the risk to be lower in the high dose range. Judging from the reports of other investigators, the RBE for chromosome aberrations in atomic bomb survivors is within reasonable limits.

ACKNOWLEDGMENT

The author wishes to express his appreciation to Dr. William J. Schull, Vice Chairman and Acting Chief of Research RERF, for his review of the manuscript and to the professional staff of the RERF Cytogenetics Laboratory for the evaluation of the chromosome data upon which this study is based.
REFERENCES

1. F.G. Spear (1953) Radiations and Living Cells. John Wiley & Sons Inc.
2. D.E. Lea (1955) Actions of Radiations on Living Cells (2nd Ed.). University Press, Cambridge.
3. H.J. Evans (1962) Chromosome aberrations induced by ionizing radiations. Int. Rev. Cytol., 13: 221-321.
4. United Nations (1969) Radiation-induced chromosome aberrations in human cells. In Report of United Nations Scientific Committee on the Effects of Atomic Radiation, New York. General Assembly 25th Session, Suppl. 13 (A/7613), pp. 98-155.
5. A.D. Bloom, S. Nerishi, A.A. Awa, T. Honda and P.G. Archer (1967) Chromosome aberrations in older survivors of the atomic bombings of Hiroshima and Nagasaki. Lancet, 2: 802-5.
6. A.A. Awa, S. Nerishi, T. Honda, M.C. Yoshida, T. Sofuni and T. Matsui (1971) Chromosome- aberration frequency in cultured blood cells in relation to radiation dose of A-bomb survivors. Lancet, 2: 903-5.
7. A.A. Awa (1975) Chromosome aberrations in somatic cells. J. Radiat. Res. (Suppl.), 16: 122-31.
8. A.A. Awa, T. Sofuni, T. Honda, M. Itoh, S. Nerishi and M. Otake (1978) Relationship between the radiation dose and chromosome aberrations in atomic bomb survivors of Hiroshima and Nagasaki. J. Radiat. Res., 19: 126-40.
9. G.W. Beebe, H. Fujisawa and M. Yamasaki (1960) Adult Health Study, reference papers. A. Selection of sample. B. Characteristics of the sample. ABCC Technical Report, 10-60.
10. Research Plan for joint ABCC-JNIH Adult Health Study, Hiroshima and Nagasaki (1962) ABCC Technical Report, 11-62.
11. R.C. Milton and T. Shochoji (1968) Tentative 1965 radiation dose estimates for atomic bomb survivors, Hiroshima and Nagasaki. ABCC Technical Report, 1-68.
12. K. Sax (1940) An analysis of X-ray-induced chromosomal aberrations in Tradescantia. Genetics, 25: 41-68.
13. H.J. Evans (1967) Dose-response relations from in vitro studies. In Human Radiation Cytogenetics (Ed. Evans, H.J., Court Brown, W.M. and McLean A.S.). North Holland Publishing Company, Amsterdam, pp. 20-36.
14. A.O. Langlands, P.G. Smith, K.E. Buckton, G.E. Woodcock and J. Mclelland (1968) Chromosome damage induced by radiation. Nature, 218: 1133-5.
15. M. Otake (1976) Radiation effects on cancer mortality among A-bomb survivors, 1950-72: Comparison of some statistical models and analysis based on the additive logit model. J. Radiat. Res., 17: 262-321.
16. T. Ishimaru, M. Otake and M. Ichimaru (1979) Dose-response relationship of neutrons and gamma rays to leukemia incidence among atomic bomb survivors in Hiroshima and Nagasaki by type of leukemia, 1950-71. Radiat. Res., 77: 377-94.
17. W.J. Schull and J.V. Neel (1965) The Effects of Inbreeding on Japanese Children. Harper & Row, New York, pp. 90-113.
18. S. Jablon (1971) Atomic bomb radiation dose estimation at ABCC. ABCC Technical Report, 23-71.
19. H.J. Evans (1974) Effects of ionizing radiation on mammalian chromosomes. In Chromosomes and Cancer (Ed. German, J.). John Wiley & Sons. Inc., pp. 192-228.
20. D. Scott, A.L. Batchelor, H. Sharpe and H.J. Evans (1967) RBE for fast neutrons and dose rate studies using fast neutron irradiation. In Human Radiation Cytogenetics (Ed. Evans, H.J., et al.). North Holland Publishing Company, Amsterdam, pp. 37-52.
21. K.E. Buckton, A.O. Langlands, P.G. Smith and J. Mclelland (1967) Chromosome aberrations following partial- and whole-body x-irradiation in man: Dose-response relationships.
APPENDIX 1: MODELS AND ESTIMATION OF PARAMETERS

In a basic $c \times 2 \times m$ contingency table, the frequency of chromosomally aberrant cells ($P_{ij}$) in the $(i, j)$th cell is $x_{ij}/t_{ij}$, where $x_{ij}$ is the number of chromosomally aberrant cells and $t_{ij}$ the number of cells observed. It is assumed that the numbers of chromosomally aberrant cells, $x_{ij}$, are mutually independent binomial variates. The joint probability density function can, therefore, be expressed by

$$L = \prod_{i=1}^{c} \prod_{j=1}^{2} \prod_{k=1}^{m} \frac{t_{ij}!}{x_{ij}!} (1 - P_{ij})^{t_{ij} - x_{ij}}$$

We shall assume that the parameters $P_{ij}$ for the binomial observations, $x_{ij}$, are related to dose in the following ways:

Model I: $P_{ij} = \alpha_i + \beta_1 D_{\gamma_i} + \beta_2 D_{n_{ij}}$

Model II: $P_{ij} = 1 - \exp(-\alpha_i - \beta_1 D_{\gamma_i} - \beta_2 D_{n_{ij}})$

Model III: $P_{ij} = 1 /[1 + \exp(-\alpha_i - \beta_1 D_{\gamma_i} - \beta_2 D_{n_{ij}})]$
where \( \alpha_i \) denotes the effects of the \( i \)-th level, \( \beta_i \) the gamma response coefficient on \( D_{\gamma ij} \) (mean gamma dose), \( \beta_n \) the neutron response coefficient on \( D_{n ij} \) (mean neutron dose) in the \( (i, j) \)-th cell and \( k \) the extrapolation number of the gamma ray dose.

The three models postulate the frequency of chromosomally aberrant cells to be linearly dependent on the neutron dose but on a higher power of the gamma ray dose. In the estimation of each parameter, an extrapolation number, \( k=1, 2, \ldots, 5 \) was assumed, and the estimates obtained by the weighted least squares method were used as the initial values in the calculation of the maximum likelihood estimates. The latter were obtained by the Newton-Raphson iteration method up to a degree of accuracy of less than \( 10^{-8} \).

**APPENDIX 2: CONFIDENCE INTERVALS OF RBE**

The RBE of neutrons is simply defined as \( \phi^* = \left( \frac{\hat{\beta}_n}{\hat{\beta}_1} \right)^{1/k} \left( \frac{1}{D_n} \right)^{(1-1/k)} \) from Model II where \( D_n \) denotes the neutron dose. The variance of \( \phi^* \) is

\[
V(\phi^*) = \left( \frac{1}{D_n} \right)^{(1-1/k)} V\left( \frac{\hat{\beta}_n}{\hat{\beta}_1} \right)^{1/k}
\]

(1)

From (1) the variance of \( \phi^* \) is a monotonic function of the variance of \( \phi = \hat{\beta}_n/\hat{\beta}_1 \).

Using the asymptotic normality of maximum likelihood (ML) estimates, Ishimaru et al. point out that the asymptotic 100(1-\( \alpha \)% confidence intervals for \( \log \phi \) (say \( \log c \)) are defined by

\[
\log c - t_{n} \sqrt{V(\log c)} \leq \log \phi \leq \log c + t_{n} \sqrt{V(\log c)}
\]

(2)

where \( \log \phi = \log \hat{\beta}_n - \log \hat{\beta}_1 \), and \( t_{n} \) denotes the 100\( \alpha \)% value of a normal deviate, and \( V(\log \phi) \) is the asymptotic variance of \( \log \phi \), i.e.,

\[
V(\log \phi) = V(\hat{\beta}_1)/\beta_1 + V(\hat{\beta}_n)/\beta_n - 2 \text{Cov}(\hat{\beta}_1, \hat{\beta}_n)/\beta_1\beta_n.
\]

The estimate of \( V(\log \phi) \) is obtained by using the ML estimates \( \hat{\beta}_1 \) and \( \hat{\beta}_n \) of the parameters \( \beta_1 \) and \( \beta_n \). \( V(\hat{\beta}_1) \) denotes the asymptotic variance of the ML estimate \( \hat{\beta}_1 \), and \( V(\hat{\beta}_n) \) and \( \text{Cov}(\hat{\beta}_1, \hat{\beta}_n) \) are the asymptotic variance of \( \hat{\beta}_n \) and the asymptotic covariance of the ML estimates, respectively.

Hence, the confidence intervals of \( \phi^* \) from the inequalities of (2) are readily expressed by

\[
\left[ \left( \frac{1}{D_n} \right)^{(1-1/k)} \exp \left\{ \frac{1}{k} \left[ \log \phi - t_{n} \sqrt{V(\log \phi)} \right] \right\} \right]^{1/k} \leq \phi^* \leq \left[ \left( \frac{1}{D_n} \right)^{(1-1/k)} \exp \left\{ \frac{1}{k} \left[ \log \phi + t_{n} \sqrt{V(\log \phi)} \right] \right\} \right]^{1/k}
\]

(3).