POSSIBLE INDIVIDUAL VARIATION IN SUSCEPTIBILITY TO RADIATION-INDUCED GENETIC CHANGES

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The genetic causation of neoplasia is supported by studies on genetic and cytogenetic specificity in neoplasms [1, 2], and on predisposition to cancer in persons exhibiting the "spontaneous chromosome breakage" syndromes, such as Bloom syndrome [3], the model ionizing radiation hypersensitive disorder ataxia-telangiectasia [4], and Fanconi anemia [5]. These model disorders have linked high incidence of cancer to end-points such as hypermutability or abnormal sensitivity to the cytotoxic action of mutagens/carcinogens. While identifiable syndromes are too infrequent to contribute appreciably to variations within the population-at-large, they have demonstrated the utility of these endpoints as indicators of susceptibility. The variation we wish to discuss occurs in clinically normal persons. Examples are:

(1) Hsu and co-workers [6] studied differential sensitivity to the radiomimetic antibiotic bleomycin in lymphocytes from two cohorts: 100 normal healthy individuals and 75 cancer patients. Cultures were set up according to a standard protocol and treated with bleomycin 30 µg/ml for five hours prior to harvesting for metaphase spreads. In the karyotypic analysis each chromatid break was recorded as one break, each chromatid exchange was recorded as two breaks and chromatid gaps or attenuated regions were disregarded.

Figure 1 is the distribution of bleomycin-induced breaks per cell (b/c) from the two groups of study subjects. The mean chromatid breakage rate ranged more than 20-fold, from 0.10->2.00. These variations were deemed due to differences in repair capacity. Among normal control individuals nearly 60% showed a mean b/c in the range of 0.20-0.60 and only 12% showed a mean b/c above 1.00. In contrast, 60% of the cancer patients demonstrated a mean b/c greater than 1.00. The data suggest a clear difference in response to bleomycin-induced damage between healthy people and cancer patients. "Thus, in an environment with a high mutagen content, hypersensitive (susceptible) individuals may acquire more mutations and more chromosomal damage than the resistant ones and are more likely to develop cancer" [7].

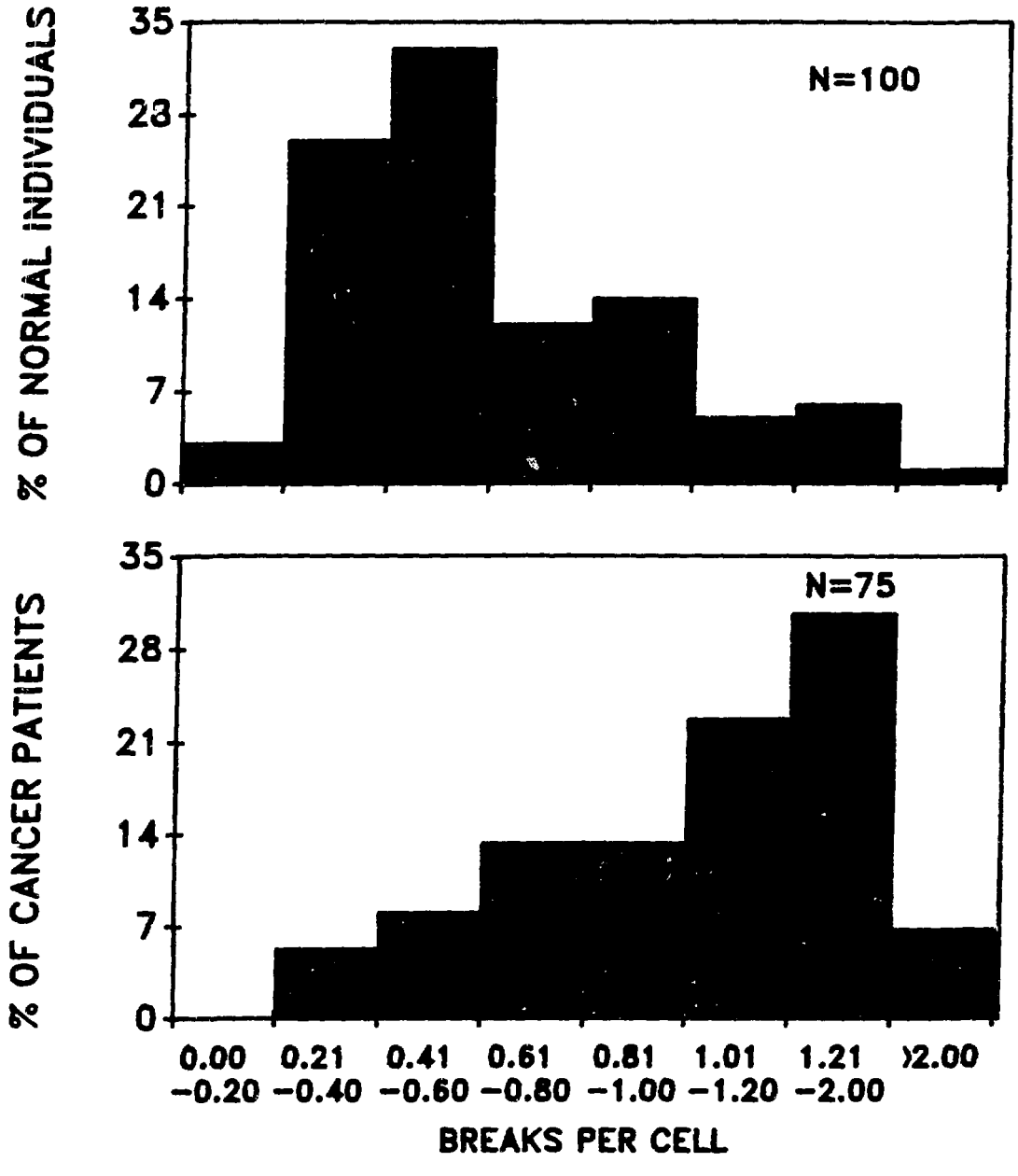

Figure 1. Distribution of bleomycin-induced breakage rates.
(Note: Data plotted from results of Hsu et al. 1985, Table 1)

(2) Inter-individual variation has been shown by Hall and Wells [8] for spontaneous and induced micronuclei frequencies in human lymphocytes. Employing a limited sample of eight individuals aged between 23 and 57 years and the cytokinesis-blocked micronucleus technique adapted from Fenech and Morley [9] the incidence of micronuclei in unirradiated control lymphocyte cultures and beta irradiated lymphocyte cultures was determined. A wide variation in dose-response was evident as depicted in Figure 2.

(3) In order to examine the range and extent of variation in radioresponse of a large population, N.E. Gentner and D.P. Morrison developed and implemented an in vitro "growback" assay. The "growback" assay measures cytotoxic response of lymphoblastoid cell lines (LCLs) to a chronic dose of Co-60 gamma-rays. Chronic dose delivery (0.003 Gy.min, 22-hour total exposure time) was used to maximize the opportunity for repair competence to contribute to a survival advantage. The radioresponse of an LCL is described by a "growback ratio" (GBR) which is the ratio of the slope of the exponential portion of the regrowth curve for unirradiated cells to the slope of the exponential portion of the regrowth curve for irradiated cells. A low GBR indicates radiosensitivity and conversely a high GBR indicates radioresistance.

LCLs from donors with disorders associated with abnormal radiosensitivity such as ataxia-telangiectasia, Fanconi anemia, Bloom syndrome and systemic lupus erythematosis ([10] and unpublished results) have low GBRs. LCLs from donors with genetic syndromes associated with hypersensitivity to carcinogenic agents other than ionizing radiation such as xeroderma pigmentosum and Tay syndrome have high GBRs [10].

The frequency distribution of GBRs for 180 ostensibly normal lines* is shown in Figure 3. The range of variation represented by these strains appears to cover the equivalent of a five-fold range of dose. Six percent or more of strains showed significant hypersensitivity; ten percent showed enhanced radioresistance.

(4) Kakati and co-workers 1985 [11], found that "the production of radiation-induced chromosomal damage varies from person to person and in the same person at different times". Blood samples were obtained from three donors. After exposure in G_0 to 0, 150 and 300 rads, standard lymphocyte cultures were set up. Dicentrics (DC) and acentric fragments (AC) were counted in M1 (first mitosis) metaphase spreads only, using sister chromatid differentiation to discriminate between M1 and second mitotic division spreads. At the highest dose, the number of DC differed significantly from individual to individual (individuals A and B, $p = 0.01$; A and C, $p = 0.005$; B and C, $p = 0.005$). Individual A

*Cell lines obtained from Chalk River Laboratory cell repository.