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STATUS OF HUMAN CHROMOSOME ABERRATIONS AS A BIOLOGICAL RADIATION DOSIMETER IN THE NUCLEAR INDUSTRY[1]

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DISCLAIMER

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Over twenty years have elapsed since we first examined chromosomal aberrations induced by ionizing radiation in human cells in culture (Bender, 1957), some 18 years since the first report of chromosomal aberration induction *in vivo* in people exposed to radiation (Tough, *et al.*, 1960), and 14 years since a serious attempt was made to use chromosome aberration frequencies as a measure of radiation dose in people accidentally irradiated in the course of their work in the nuclear industry (Bender, 1964). There have since appeared a large number of reports of aberrations in cells from persons occupationally exposed under both normal operating conditions and in accidents in various phases of the nuclear fuel cycle. Much of this information is covered in earlier reviews (UNSCEAR, 1969; Bender, 1969). Recent years have produced a wealth of new data and occasionally not without some controversy. New cytogenetic techniques have appeared, and some are clearly very useful for both routine monitoring and biological dosimetry. Chromosomal aberration analyses are now coming into wider use in various phases of the nuclear industry (though they are still not as widespread as I would like to see). What I shall attempt here is not a comprehensive historical review, but rather a critical review of our progress in the application of cytogenetics to the problem, the factors influencing its utility, and its prospects for what I hope will be its much wider application in the future.

BACKGROUND

Though the development of techniques allowing the study of human chromosomes is more recent, the direct microscopic study of the induction of chromosomal breaks and rearrangements by ionizing radiation dates back four decades (Sax, 1938), and an impressive body of both data and theory has grown up since. Though mostly developed with plants and non-human animal materials, much of what has been learned is directly applicable to

human radiation cytogenetics, and must often be used to fill in the gaps where we lack direct human experience. A very brief outline of our general understanding of aberration induction by ionizing radiation is useful in evaluating some of the problems of human radiation cytogenetics.

1. Aberration Types

Three general classes of chromosomal aberrations are induced by irradiation of cells, depending upon their stage in the cell cycle when irradiated. With one notable exception (to which I shall return), irradiation during the pre-DNA-synthesis (G_0 or G_1) phase induces only aberrations of the chromosome type, characterized by breakage and rejoining that involves both chromatids when the chromosomes are viewed at the succeeding metaphase. When the irradiation is administered later in the interphase, beginning just prior to the demonstrable onset of DNA synthesis (S) and continuing through the S and post-DNA synthetic (G_2) phases, chromatid aberrations, usually involving one of the two chromatids of a chromosome, are induced. The exception is the isochromatid deletion, which involves isolocus breaks in both chromatids, but may often be distinguished from the chromosome type deletion because of sister union, a phenomenon not occurring with chromosome breaks induced earlier in the cell cycle. Interestingly, though not at present of any practical significance in human radiation cytogenetics, a third class of aberration, the half-chromatid exchange, is induced when cells are irradiated during the mitotic or meiotic prophase. Though the theory is by no means proven as yet, one interpretation of the mechanism of aberration induction by radiation (Bender, Griggs and Bedford, 1974) is that the chromosome or chromatid break represents a DNA double polynucleotide strand break and that rejoining of breaks to form more complex

aberrations involves interaction between "sticky ends" formed enzymatically at the broken ends. The exception to the rule of G_1 induction only of aberrations of the chromosome type occurs in cells from individuals afflicted with the inherited disease ataxia telangiectasia, where apparently because of a defect in DNA repair, G_1 irradiation induces significant yields of aberrations of the chromatid type (Taylor et al., 1976).

Though elementary, the distinction between aberrations of the chromosome and of the chromatid types is not without practical significance for chromosomal dosimetry. Under ordinary circumstances, irradiation of the most commonly used human cell, the circulating peripheral lymphocyte, which is in the G_0 phase while in the circulation, will yield only aberrations of the chromosome type. This is not the case, however, for most chemical clastogens (Bender, Griggs and Bedford, 1974), which instead induce aberrations of the chromatid type only, even when G_0 or G_1 cells are exposed. Thus increases in peripheral lymphocyte chromosome type aberration levels may unequivocally be attributed to radiation exposure (exposures to the chemicals like bleomycin that form the rare exception to the general rule may usually easily be excluded), and increases in chromatid aberration levels must be attributed to some other cause.

Whether of the chromosome or the chromatid type, aberrations may be further categorized as simple breaks (deletions) or as aberrations involving rejoining between two or more broken ends. The latter may be either symmetrical (inversions and translocations) or asymmetrical (rings and dicentrics). These distinctions are of practical significance in several ways. Deletions and asymmetrical exchanges produce acentric fragments, but symmetrical exchanges do not. Acentric fragments and asymmetrical exchanges tend to disappear from cell populations as a result of cell divisions

intervening between induction and observation; symmetrical exchanges do not. Just as important, the dose-effect kinetics for aberration induction and the effects of dose rate and radiation quality (LET) are different for simple breaks and for exchange-type aberrations.

2. Dose-Effect Kinetics

The shapes of the dose-effect curves observed for induction of simple breaks and of exchange aberrations by acute doses of low LET radiations such as γ rays are quite different. Yields of the former are a more-or-less linear function of dose, often written:

$$Y = C + \alpha D,$$

where Y is yield, C the spontaneous frequency, D the dose and α the coefficient of aberration production, a proportionality constant. Yields of two-break aberrations, on the other hand, approach being proportional to the square of the dose, as:

$$Y = C + \beta D^2,$$

where β is the coefficient of two-break aberration production. More generally, because there is normally some "two hit" component in simple break yields and some "single hit" component in that of exchanges, the expression:

$$Y = C + \alpha D + \beta D^2$$

is often written; β is simply quite small for simple breaks and α quite small for two-break aberrations for acute low LET radiations.

Though this simple linear-quadratic model is often used and is easily interpreted in simple biological terms, it is worth noting that modern

microdosimetric theory predicts that the curves for even simple events like single chromosome breaks should depend to some extent upon the square of the dose (Kellerer and Rossi, 1971). The microdosimetric expression is:

$$\varepsilon = \kappa\ (\zeta D + D^2),$$

where ε is effect, ζ is a physical quantity related to the dose average specific energy deposited in the target volume by individual ionizing events, and κ is a "sensitivity coefficient" proportionality constant. Obviously, the microdosimetric expression reduces to the more familiar linear-quadratic form if

$$\alpha = \kappa\zeta,$$

and

$$\beta = \kappa.$$

3. Dose Rate and Fractionation

The effect of decreasing the rate at which a dose of low LET is administered is to decrease the importance of the dose-square component of the dose-effect curve. At very low dose rates the dose-square, or β term disappears entirely, and only the linear, or α term remains. Fractionation of doses has a like effect: as the interfraction interval increases the total yield approaches the sum of the yields from each of the fractions alone. The interfraction interval required to reach complete additivity is generally of the order of a few hours. These phenomena are believed to result because the individual lesions that interact to produce the dose-square component are available for such interaction only for a limited time, so that if a dose is sufficiently protracted, there is little or no chance that a second lesion will be induced in a cell already containing

one that is still available. From the practical point of view the dose rate and fractionation effects tend to reduce the sensitivity of chromosomal aberration monitoring in routine occupational exposures. However for doses so low that the dose-square component makes little contribution to yield, a few tens of rads for practical purposes, the effect is of no consequence.

4. Linear Energy Transfer and Relative Biological Effectiveness

Though some dose-square component is the rule for acute low LET doses, there is little or no dose-square component when the radiation is of high LET, as in the case of the protons resulting from fission neutron exposures or of α particles from plutonium or uranium and thorium decay products. For such radiations simple linear dose-effect curves are observed, at least up to the point at which saturation occurs. This is generally interpreted to result from the large amount of energy that tends to be deposited in any nucleus traversed by a particle.

High LET radiations also tend to be more efficient producers of aberrations than those of low LET; that is, their relative biological effectiveness is high. For acute doses, since the low LET curves tend to be a greater than linear function of dose, there is obviously no single value for RBE (i.e., since RBE is the ratio of slopes, and the slope of the low LET curve changes as a function of dose, RBE is also a function of dose). As either dose or dose rate is diminished, however, and the low LET dose-square term diminishes, RBE approaches a constant, large value that is simply the ratio of the high LET slope to the α term of the low LET curve. The absolute value of this "ultimate RBE" can be as high as of the order of 100 (Neary, et al., 1963). The low dose, low dose rate case is, of course, that pertinent to chromosomal monitoring of the majority of routine occupational exposures in the nuclear industry.

5. Other Factors Influencing Aberration Yields

Chromosomal aberration yields may be expected to be modified by a number of spatial and temporal factors, including the time following a radiation exposure at which cells are examined. As already mentioned, cell divisions intervening between aberration induction and sampling result in the loss of some classes of aberrations from the population. Acentric fragments tend to be lost because of their failure to attach to the spindle apparatus. Dicentric chromosomes may form anaphase bridges and thus prevent completion of cell division, while many acentric ring chromosomes are unstable, with exchanges between chromatids leading to dicentric or interlocked chromatids that cannot separate normally at anaphase. Thus the frequency of such aberrations decreases rapidly over the course of a few cell cycles in dividing cell populations (Conger, 1965; Sasaki and Norman, 1967; Minkler, et al., 1971; Bedford, et al., 1978). Symmetrical exchange aberrations such as inversions and reciprocal translocations, on the other hand, encounter no such mechanical problems during segregation, and tend to remain in cell populations over long periods.

Non-uniform distribution of radiation dose naturally also influences not only total aberration yields in the cell population sampled, but also the relative frequencies of the different aberration types and their distribution among cells. Obviously, aberrations are induced in individual cells in proportion to the individual doses the cells receive, so yields are reduced if some of the population receive less than the maximum dose. In extreme cases the presence of a large fraction of cells exposed to little or no radiation markedly disturbs the expected Poisson distribution of aberrations among cells. In situations where aberration dose-effect curves display a large dose-square component, as for exchanges induced by acute,

low LET irradiation, the relative frequencies of simple breaks and exchanges will also be distorted by non-uniform dose distribution with respect to what would be observed if the average dose were actually received by each cell in the population. Such influences become particularly important where the radiation has only a short range in tissue, as for soft beta or alpha particles, and can be particularly acute for locally deposited radionuclides, a situation of obvious importance in occupational exposures in the nuclear industry.

All of these factors may be expected to influence the ways in which chromosomal aberration monitoring is useful in the nuclear industry, some making quantitative biological dosimetry difficult, but others actually making the system more useful for answering some of the questions that often arise in the case of accidental radiation overexposures.

HUMAN CELLS IN VITRO

Early experiments with human cells irradiated in vitro rapidly confirmed the applicability of many of the basic principles of radiation cytogenetics outlined above to the special (from our point of view, at least) case of human chromosomes, first for diploid tissue cultures and later, when the peripheral lymphocyte short term culture technique became available, for this system as well. The earlier work has been extensively reviewed (Evans, Court Brown, and McLean, 19671; Bender, 1969; UNSCEAR, 1969). However, and perhaps unavoidably, several areas of substantial controversy have developed as a result of the lymphocyte studies. Both appear to involve complexities of the peripheral lymphocyte culture system itself, and not, in fact, to constitute any significant deviation of human chromosome response to ionizing radiation from that which would be anticipated from earlier experience with non-human material.

One discrepancy involved substantial variations in the absolute aberration yields observed per unit dose when different laboratories measured

the yields of aberrations in cultures acutely irradiated with low LET radiations. Some of the difference pretty clearly resulted from differences in aberration scoring criteria in different laboratories (Abbott, et al., 1974), much clearly arose because of differences in the speed with which lymphocytes completed cell cycles under the different culture conditions used in different laboratories, together with failure to anticipate the influence that the presence of second and later post-irradiation division cells might have on aberration yields (Buckton and Pike, 1964, Sasaki and Norman, 1966; Heddle, Evans and Scott, 1967; Sharpe, 1969), and some probably resulted from physical differences between experiments (Bajerska and Liniecki, 1969b; Scott, et al., 1969; Brewen and Luippold, 1971; Purrott and Lloyd, 1973). Some, however, clearly results from the more subtle influences of differential radiosensitivity and radiation-induced delays in lymphocytes arriving at their first metaphases after different times in culture (Bender and Brewen, 1969; Buckton, et al., 1971; Steffen and Michalowski, 1973; Lloyd, Purrott and Dolphin, 1973; Santos Mello, Kwan and Norman, 1974).

The other discrepancy appeared when it was reported that in contrast to the classical finding that two-break aberration induction by acute doses of low LET radiation is a marked function of the square of the dose, the dose-effect curve for rings and dicentric induction in human lymphocytes irradiated in vitro was a virtually linear function of dose (Mouriquand, et al., 1966; 1971; Evans, 1967a, b, 1968; Heddle, Evans and Scott, 1967; Sevankaev and Bochkov, 1968). This peculiar result, which also led to some curious dose fractionation results (Evans, 1966; 1967c, d), in marked contrast to the prior confirmation by others that the expected large dose square component was also observed in human lymphocytes (Bender and Gooch,

1962a; Gooch, Bender and Randolph, 1964; Norman, et al, 1964; Kelly and Brown, 1965; Norman and Sasaki, 1966; Visfeldt, 1966). However, a careful replication of one of the anomalous experiments failed to confirm the result (Bender and Barcinski, 1969), and several dose-effect curves reported since have shown large dose-square components (Brewen and Luippold, 1971; Bauchinger, 1971, Buckton, et al., 1971; Brown and McNeill, 1971; Todorov, et al., 1972; Wolf, 1972; Brewen, Preston and Littlefield, 1972; Lloyd, Purrott and Dolphin, 1973a; Purrott, et al., 1975). Since the difference has not been satisfactorily explained, it appears that this must be regarded simply as one of those anomalies that turn up from time to time, and taken into account where necessary. A similar anomaly, the finding of a substantial dose-square component for aberration induction by chronic, low LET irradiation (Scott, et al., 1970), also appears to have been a local peculiarity, since a subsequent study failed to confirm it (Brewen and Luippold, 1971).

One consequence of the differences in aberration yields obtained by various laboratories, and in particular the contribution of differences in dose-effect kinetics, has been to emphasize the need for careful control of the conditions under which they are measured in the peripheral lymphocyte system. A major use of in vitro determinations has been to provide "calibration" of the lymphocyte chromosomal aberration technique as a means of biological dosimetry, especially in cases of accidental substantial whole body radiation exposures. For such purposes it is now widely appreciated that the coefficients of aberration production used should if possible be obtained by the same laboratory under the same conditions as for the determinations of in vivo aberration yields. However, where local determinations are unavailable, there is little choice but to use published coefficients of aberration production, taking care that those selected are for the appropriate irradiation and

culture conditions.

In addition to the large number of determinations that have been published for acute, low LET exposures, there are also several available for low dose rate, low LET exposure, providing independent estimates of the value of α, the coefficient of greatest importance for much of the chromosomal aberration monitoring in the nuclear industry (Bajerska and Liniecki, 1969; Brewen and Luippold, 1971; Liniecki, Bajerska and Jankowski, 1971). Though a good deal more information for high LET radiations would clearly be desirable, particularly for alpha particles, there are several published coefficients for in vitro irradiation of human lymphocytes with neutrons of various energies (Gooch, Bender and Randolph, 1964; Scott, et al., 1967, 1969; Dolphin and Purrott, 1970; Biola, et al., 1970; Todorov, et al., 1973; Dolphin, et al., 1973; Vulpis, 1973), and one for high energy protons (Todorov, et al., 1972).

THERAPEUTIC IRRADIATIONS

Several laboratories have measured lymphocyte aberration frequencies shortly after patients underwent whole body x-irradiation, and the results are of use in confirming at least to some extent the applicability of in vitro data to the problems of chromosome aberration monitoring in the nuclear industry, even though such irradiations are, of coures, of already ill persons whose response could differ from that of healthy persons. Sasaki, Ottoman and Norman (1963; Norman, et al., 1964) studied two patients given single, whole-body x-ray doses of 300 R, and obtained yields not strikingly different from those their laboratory obtained for in vitro lymphocyte irradiation. Buckton, et al. (1967, 1969, 1971) and Langlands, et al., (1968) studied a series of cancer patients given single, whole body doses of 2 MeV x-rays. For reasons I have outlined elsewhere (Bender, 1969), I believe the resulting lymphocyte aberration frequencies are not in serious disagreement with what

would be expected from their laboratory's in vitro results, though the authors originally took a somewhat different view.

DOSIMETRY IN RADIATION ACCIDENTS

The possibility of using direct cytological measurements of chromosomal aberration frequency as a biological dosimeter was appreciated very early by Marshak and Hudson (1937), who used the percentage of abnormal anaphases in onion root tip cells as a measure of x-ray dose. With the advent of human radiation cytogenetics using peripheral lymphocytes, P.C. Gooch and I made a detailed proposal that the technique be applied with peripheral lymphocytes from irradiated people (Bender and Gooch, 1962a), and this method has also been strongly recommended many others working in a number of laboratories around the world as well (Kelly and Brown, 1965; Sugahara, et al., 1965; Biola and LeGo, 1966, Aleksie, et al., 1967, Norman, et al., 1967; Sasaki, 1968; Vulpis and Strambi, 1969; Bauchinger, Schmid and Hug, 1970; Dolphin and Purrott, 1970; Evans, 1970; Dolphin, Lloyd and Purrott, 1973; Dolphin and Lloyd, 1974). The technique has now been accepted as a relatively standard proceedure, and has proven especially useful for radiation accidents in which substantial, essentially whole body, acute exposures were received.

P.C. Gooch and I made the first attempt at quantitative human chromosomal aberration dosimetry I know of, in connection with the "Recuplex" criticality accident at Hanford, Washington in 1962 (Bender, 1964; Bender and Gooch, 1966), in which three workers were exposed to a mixture of gamma and fission neutron irradiation. At least fourteen cases where quantitative aberration dosimetry was attempted are now in the open literature; generally the results are in reasonable agreement with the (sometimes scant) physical evidence of radiation dose, and certainly they seem to me to confirm the general utility of the technique.

1. Low LET Irradiations

There have been relatively few (fortunately) acute, reasonably whole body human radiation exposures since we have acquired the ability to make prompt peripheral lymphocyte aberration frequency determinations. Some have been exposures to low LET X or gamma rays, and some to mixtures of low and high LET radiations. The former are considerably easier to interpret. P.C. Gooch and I studied three men who received moderate gamma ray doses in a 1962 accident at the Puerto Rico Nuclear Center (Bender, 1964, 1969). The doses were estimated to range from about 17 to about 57 rad. The aberration frequencies observed in cultures from blood samples obtained three days after the accident produced dose estimates in reasonable agreement with the physical estimates, considering the large physical uncertainties involved.

Schneider, Chone and Blonnigen (1969) investigated lymphocyte aberration frequencies in a blood sample obtained two days after an accidental irradiation with an ^{192}Ir radiography source. The physical dose estimate was 100 rad. Based upon ring and dicentric yields, they estimated a dose of 122 rad from the aberration coefficients of Bender and Gooch (1962a); using deletions the estimate was 104 rad. Considering the likely inhomogeniety of dose distribution, this is really remarkably excellent agreement.

Dolphin, et al., (1970) investigated an accident in 1969 in which two men were irradiated with a ^{60}Co radiographic source. The physical dose estimates were 16-39 rad and 18-49 rad. Aberration analyses on peripheral lymphocytes obtained eleven days later yielded biological dose estimates of 43 (35-65) and 24 (12-40 rad based upon dicentric frequencies and aberration coefficients obtained in their own laboratory. Again, agreement is remarkably good.

Brown and McNeill (1971) studied aberration frequencies in peripheral lymphocytes obtained 8 and 21 days after two persons were accidentally irradiated with a ^{192}Ir source. A film badge dose of 22 rem was obtained for one subject; the other was estimated to have received less exposure. Based upon dicentric frequencies, both men were estimated to have received 29 rem, an estimate not at all out of line with the physical estimates.

Brewen, Preston and Littlefield (1972) carried out an extensive investigation of lymphocyte chromosomal aberration yields in a man accidentally exposed to an acute dose of ^{60}Co gamma rays at an Oak Ridge experimental facility designed for the whole body irradiation of large animals. The dose, however, was not really homogeneous over the victim's body. Physical estimates yielded an average midline dose of 127 R. Chromosomal aberration frequencies determined on seven peripheral lymphocyte samples obtained from 6 hr to 32 days after the accidental irradiation yielded biological dose estimates of 144 R based upon rings and dicentrics and 135 R based upon deletions, using coefficients determined from an in vitro leukocyte experiment using ^{60}Co gamma rays. For this case, like the others, I find the agreement between physical and biological dose estimates very impressive indeed.

2. Irradiations in Criticality Accidents

Accidental radiation exposures involving a criticality, either from a nuclear reactor or occurring during the handling of enriched uranium or plutonium, though less frequent than low LET accidents, have also provided some opportunity to test the utility of peripheral lymphocyte chromosome aberration analyses as a means of biological dosimetry. Since such accidents involve exposure to a mixed flux of gamma rays and fission spectrum neutrons, however, there is the large uncertainty of having to deal with two sets of aberration induction coefficients with, at least as found by many laboratories,

differing dose-effect kinetics as well. Nevertheless, I personally find our accumulated experience reassuring.

P.C. Gooch and I obtained peripheral blood samples from three men irradiated in the "Recuplex" criticality accident at Hanford in 1962 and attempted chromosomal aberration dosimetry (Bender, 1964; Gooch, Bender and Randolph, 1964; Bender and Gooch, 1966). The physical dose estimates were 47, 23 and 12 rads respectively, for the three men, of which roughly half was contributed by neutrons. The aberration frequencies for samples obtained during the first four weeks following the accident yielded dose estimates, based on coefficients obtained in our in vitro x-ray and neutron experiments, of 11 and 30, of 4 and 37, and of 2 and 2 rads, based upon the deletions and upon the rings and dicentrics, respectively.

LeGo (1967) studied chromosomal aberrations in a man irradiated in an accidental criticality at Mol in 1965. From aberration data on leukocytes from the victim, and using published aberration coefficients (Bender and Gooch, 1962a; Kelly and Brown, 1965), LeGo made an estimate of between 470 and 500 gamma-ray-equivalent rads, a result not in serious disagreement with the physical dosimetry available.

Lejeune, Berger and Levy (1967) determined the yields of aberrations in peripheral lymphocytes obtained two days and 31 days after the accident from a person exposed to a mixed dose estimated at 33 rads of gamma rays and neutrons from a proton beam. From the pooled deletion frequency in the two samples, using the coefficients of Bender and Gooch (1962a, 1966), it is possible to estimate a dose of about 60 gamma-ray-equivalent rads.

3. Delayed Sampling

Several studies have found that peripheral lymphocyte aberration yields tend to remain essentially unchanged for the first few weeks following

a reasonably whole-body radiation exposure (Bender and Gooch, 1966; Bender, 1969; Brown and McNeill, 1971; Brewen, Preston and Littlefield, 1972). After about four weeks (a point corresponding roughly to the nadir in the lymphocyte count in persons exposed to moderate doses) the lymphocyte aberration frequencies generally decrease, and the proportion of cells containing exchanges but lacking the expected acentric fragments increases (Bender and Gooch, 1966; Lejeune, Berger and Levy, 1967; Bender, 1969; Brewen, Preston and Littlefield, 1972). Cells with aberrations continue to be seen for many, many years following substantial exposures however (Bender and Gooch, 1962b, 1963; Buckton et al., 1962; Goh, 1966, 1968; Littlefield and Joiner, 1976; Pendic, Barjaktarovic and Kostic, 1978).

The practical consequence of the observed aberration loss with increasing time between irradiation and sampling is, of course, that for accidental overexposure monitoring one may apparently be confident that peripheral lymphocyte aberration yields from blood samples obtained within a few weeks after exposure will be useful. Because too little information on the time course for the frequencies of the various aberration classes after this initial period is as yet available, only rather crude estimates of the sorts of doses that might have actually been received can be made from later blood samples. However, even these may be useful on occasion, as where a chronic overexposure condition eventually results in some clinical manifestation such as radiodermatitis (Mouriquand, et al., 1964; Lloyd, Purrott and Dolphin, 1973b).

4. Anomalies In Relative Aberration Frequency and Distribution

As noted earlier, distortion of the relationship between deletions and two-break aberrations and of their distribution among cells, is expected to result if the distribution of dose is markedly inhomogeneous, or if the

radiation is of only a portion of the body. Because of the difference in dose-effect kinetics, high LET radiations also may produce a different relationship between single-and multiple-break aberrations from that observed for low LET radiations. While this often introduces complications in the interpretation of lymphocyte aberration results, it can also often be useful in the case of accidental radiation exposures. Often it is known either that the irradiation could not have included a high LET component, or that the dose must have been reasonably uniformly distributed over the whole body. In such cases useful information regarding an accident can sometimes be deduced from the aberration data. P.C. Gooch and I made such a deduction in the case of two men who received low radiation doses during the "clean up" after a criticality accident, where the gamma dose from the fission products must have been relatively uniformly distributed (Bender, 1969). The men were not present during the critical excursion, and thus should not have been exposed to high LET radiation. However, we observed two-break aberration frequencies that were higher than expected in relation to the deletion frequencies, and concluded that there must in fact have been some high LET exposure. Physical evidence later confirmed that there had indeed been a second, low level critical excursion while the men were present.

I have also on occasion deduced markedly nonuniform dose distribution from aberration data, as, I am sure, have others as well. In one case, for example, a worker was accidentally exposed to x-rays when an industrial radiographic machine safety interlock malfunctioned. The physical reconstruction suggested a reasonably uniform exposure, but the aberration data did not. Questioning of the victim then elicited the until-then-forgotten fact that he had actually spent much of the time during the exposure upon a stepladder in such a position that most of the dose was actually to his

lower body (and much of it not "seen" by the film badge worn at his waist).

5. The "Black Badge"

A situation in which chromosomal aberration determinations have proven especially useful is that in which an overexposure is indicated by a film badge or other dosimeter, although the opportunity for such an exposure seems lacking, or where the nature of the evidence from the badge itself suggests the subject was not actually wearing it when it was exposed. Though the absence of chromosomal aberrations in a peripheral lymphocyte culture is only evidence of a negative sort, it often provides useful reassurance. Because the results in such cases are negative, they tend not to be reported in the scientific literature. Nevertheless, not only have I had a number of such cases myself, but I have also received anecdotal information on a number of others, so they are not at all uncommon. Furthermore, the large number seen by the Harwell group over the years (Purrott, et al., 1972, 1973, 1975) leaves little doubt either as to the general utility of aberration determinations in such cases, or as to the frequency of such situations in the nuclear industry.

ROUTINE OCCUPATIONAL EXPOSURES

There have been a number of studies reported of lymphocyte chromosome aberration frequencies in occupationally radiation exposed groups. Their exposures, of course, are more or less chronic and low level, though they may actually be made up of a series of small acute exposures in some cases. Some years ago I characterized the results of some of these studies as generally agreeing in demonstrating small increases in "radiation worker" populations in comparison with control populations (Bender, 1969). Studies coming to my attention since, for example those of Ruffie, et al., (1964), Markovic and Panon (1968), Pendic (1968); Brown and McNeill (1969),

Sevanjkayer, Bykhovsky and Bochkov (1969) and Popescu and Stefanesceu (1971), as well as the data reported by the Harwell group (Purrott, et al., 1972, 1973, 1975), are in general agreement; statistical increases have been demonstrated, particularly where the occupationally exposed group has been selected for high cumulative exposure. Some individuals clearly do display elevated aberration levels, usually of uncertain origin, but generally speaking the aberration levels seen in lymphocytes from most individuals in the routine occupational exposure groups have, reassuringly, not been significantly elevated over those of control individuals.

I thus appears that in view of the fairly large expense involved in scoring chromosome preparations for aberrations, it would be difficult to justify the performance of routine chromosome aberration analyses generally for worker populations in the nuclear industry, though pre-exposure control lymphocyte samples or cultures that could be scored later should the need arise might be of value, especially for high risk occupations (interestingly, though, at least one large industrial chemical firm in the United States has initiated a large scale program of cytogenetic screening of its employees (Kilian, Picciano and Jacobson, 1975; Kilian and Picciano, 1976).

INTERNAL RADIONUCLIDE EXPOSURES

Internal exposures resulting from ingestion or inhalation of various radionuclides are, of course, often contribute to some degree to the radiation exposures of workers in various phases of the nuclear industry. The alpha particle emitters encountered in uranium mining and milling, in fuel fabrication, and in reprocessing are of particular concern. There exists a good deal of evidence from groups exposed to such radionuclides outside of what might properly be included as the nuclear industry, such as thorotrast patients (Fischer, et al., 1966, 1967; Buckton, Langlands

and Woodcock, 1967), radium dial painters (Wald, et al., 1962; Boyd, et al., 1966, 1967; Tuscani and Muller, 1967; Hoegerman, et al., 1975) and others exposed to radon or thoron naturally (Penna Franca, et al., 1965; Barcinski, et al., 1975) or accidentally (Pohl-Ruling, Fischer and Pohl, 1976; Todorov, et al., 1970). Wald, Koizumi and Pan (1967) studied workers with ^{125}I burdens. Generally, such studies have shown that there are indeed increased lymphocyte aberration frequencies in cases where there are substantial body burdens of alpha emitting radionuclides, that aberrations tend to be quite non-randomly distributed among cells, with a few cells tending to have multiple aberrations, that the frequency of multiple-break aberrations tends to be high relative to single breaks and that there is at least a very crude correlation with body burden.

Two groups occupationally exposed in the nuclear industry to internal alpha emitters have also been studied. These are uranium miners and plutonium workers.

1. Uranium miners

MacDiarmid, et al., (1968), Kilibarda, Markovic and Panov (1968) and Brandom, et al. (1972, 1978) have studied the frequencies of chromosomal aberrations in lymphocytes from underground uranium miners. MacDiarmid, et al. and Brandom, et al., in their first investigation included 6 and 15 miners with estimated cumulative exposures of between 1497 and 4531 work level months (WLM) and between 10 and 5400 WLM, respectively. Kilibarda, Markovic and Panov studied 20 miners exposed to radon levels of between about 4×10^{-10} and 3×10^{-9} Ci per liter of air. The studies of MacDiaarmid, et al., of Kilibarda, Markovic and Panov and the first of Brandom, et al. all involved determination of aberrations in non-banded conventionally stained preparations. Both the studies of MacDiarmid, et al., and that of Brandom, et al.

demonstrated increases in aberration levels among the miners as compared with the controls. Rings, dicentrics and symmetrical exhanges were seen as well as simple deletions. No clear relation between exposure and the presence of chromosome aberrations could be seen, however. The study of Kilibarda, Markovic and Panov, on the other hand, was negative.

In their second study, Brandom, et al., used G-banded preparations in order to better ascertain the frequency of symmetrical exhanges. An impressive total of almost 7,500 cells from 80 miners were examined. When the subjects were assigned to broad WLM exposure categories and the aberration data pooled, a significant regression of the frequency of aberration frequency on exposure was seen. Interestingly, however, the yields per WLM tended to decrease with increasing exposure. It thus appears that although the presence of cells with aberrations is generally increased among miners, their frequency is not a straightforeward function of exposure, and that the aberration technique can only serve at present as a qualitative sort of dosimeter.

2. Uranium milling

There appears to be no information in the literature on lymphocyte aberration frequencies in workers in uranium milling operations, although at least in the early days such mills seem to have provided the opportunity for exposures, particularly to dust in the mill air. I recently examined lymphocytes from a man whose work history included employment in a uranium mill during the 1940's, and among a sample of 200 cells found one that contained 3 dicentrics, 2 rings and 2 deletions, and another with 2 deletions and a dicentric. Though not conclusive by any means, this does seem consistent with the possibility of internal alpha particle emitters, and suggests to me that further study of mill workers might be profitable.

3. Plutonium Workers

Brandom, et al., (1978) have presented extensive data on lymphocyte aberration levels in workers at the Rocky Flats, Colorado facility that had measured body burdens of plutonium. A staggering total of just under 40,000 cells from 343 workers were analyzed using G-banding for "complex" aberrations. As with the uranium miners, there was a crude regression of aberration frequency on estimated Pu body burden, but the yield was less per nannocurie of estimated body burden for the larger burdens than for the smaller ones. Several explanations for this phenomenon seem possible, but without further information it appears that cytogenetics can provide only the relatively qualitative indication of "dose" that it does in the case of other internal alpha particle emitters.

SUMMARY

In conclusion, it seems to me that determination of peripheral lymphocyte chromosome aberration levels is now firmly established as a means of biological dosimetry of great value in many phases of the nuclear industry. In the case of large external exposure it can provide valuable quantitative estimates, as well as information on dose distribution and radiation quality. In the case of routine occupational exposures the technique is more qualitative, but if of value particularly in resolving uncertainties as to whether suspected overexposures did in fact occur. Where workers accumulate burdens of internal emitters, aberration analysis provides a valuable, though at present quite qualitative indicator. In spite of the expense of cytogenetic analyses, I personally believe that they are of sufficient value to justify much more widespread application, particularly in high risk situations.

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