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Genetics

"Rogue" lymphocytes among Ukrainians not exposed to radioactive fall-out from the Chernobyl accident: The possible role of this phenomenon in oncogenesis, teratogenesis, and mutagenesis

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ABSTRACT **Cultured lymphocytes exhibiting extreme cytogenetic damage (rogue cells) were observed in preparations from 8 of 24 individuals sampled in Krasilovka, a Ukrainian village receiving little or no increased radiation after the Chernobyl disaster, but were not observed in an additional 24 persons from two Russian towns in the more contaminated area. This observation cements the worldwide occurrence of these cells. The present data plus a review of the literature establish that rogue cells appear in brief bursts simultaneously in certain individuals of discrete populations. We suggest that the pattern is consistent with the action of a viral trigger that acts directly or indirectly—the latter possibly through the activation of latent chromosomal retroposons. If this phenomenon occurs in other tissues, it may have important implications for oncogenesis, teratogenesis, mutagenesis, and evolution.**

In recent years a number of reports (1–4) have described the occurrence of highly abnormal karyotypes, which we have termed rogue cells (4), among cultured lymphocytes from apparently normal Amerindians, Englishmen, and Japanese. In the fall of 1990, under the auspices of a study of the after effects of the Chernobyl nuclear accident coordinated by the International Atomic Energy Agency, we conducted a cytogenetic analysis of cultured lymphocytes from 48 blood samples from residents of the Russian and Ukrainian Republics of the then U.S.S.R. The present communication will report on the results of this analysis, with particular reference to the finding of rogue cells in 8 of these individuals. Since these cells were, in this study, found only in individuals thought to have received little or no increased radiation at the time of the Chernobyl accident, the question of a radiation effect does not seem pertinent. We will then combine these data with previous findings to develop an understanding of the epidemiology of the rogue-cell phenomenon and to explore some of its possible implications for oncogenesis, teratogenesis, mutation, and evolution.

SPECIMENS AND METHODS OF STUDY

The 48 blood samples analyzed in this study, all obtained in September 1990, were evenly divided with respect to the radiation histories of their donors. Twenty-four of the samples were obtained from persons exposed to moderate fall-out from the Chernobyl accident of 1986 in the villages of Novozybkov (population, 49,400; 14 samples) and Zlynka (population, 5600; 10 samples) in the Russian Republic. These villages are some 170–180 km north–northeast of Chernobyl. Of the remaining 24 samples, 23 were obtained from persons exposed to minimal if any fall-out from the accident who lived in the small village of Krasilovka (population, 2500) in the Ukrainian Republic, some 30 km southwest of Chernobyl. One sample (in which a rogue cell was subsequently observed) obtained in Krasilovka was from a visitor from the uncontaminated town of Kozelec, ≈80 km to the east of Krasilovka. The mean age was 45.0 ± 8.8 years for the Novozybkov–Zlynka sample and 45.9 ± 9.6 years for the Krasilovka sample. All samples were drawn into Vacutainers containing heparin as anticoagulant and refrigerated promptly on ice; the samples were 4–6 days in transit to the Radiation Effects Research Foundation's Cytogenetics Laboratory in Hiroshima.

Lymphocytes were cultured for 48 h, then harvested, and Giemsa-stained. The protocol has been described elsewhere (5); current modifications are the use of RPMI 1640 medium as the culture medium and the addition of Colcemid (0.2 μg/ml) after the first 24 h of incubation. This protocol is designed to study the first postculture mitotic metaphases. [We are indebted to Thomas Glover (personal communication) for reminding us that most laboratories harvest cultured lymphocytes after two or three cell divisions, by which time most rogue cells would presumably be lost.] The protocol called for scoring 200 cells from each subject; this was not possible in four cases. All preparations were coded with respect to the individual's exposure status while they were being read.

Fourteen months after these slides had been stained and mounted, we attempted to apply the fluorescent *in situ* hybridization staining technique (6) to the slides exhibiting rogue cells to understand better the precise pattern of chromosomal damage. Reagents consisted of the Spectrum Orange WCP DNA probes 1 and 12 of Imagenetics (Napierville, IL), used as recommended by the company. In addition, we are grateful to Imagenetics for the gift of the newly developed Spectrum Green WCP DNA probe 4. Unfortunately, although the staining was quite satisfactory for freshly prepared unmounted slides, we could not obtain satisfactory results with this older material, despite multiple attempts to dissolve the mounting medium from the slide after the coverslip had been removed.

FINDINGS

The cytogenetic findings are summarized in Table 1. The observations are presented under three headings, cells with unstable aberrations, cells with stable aberrations, and rogue cells. Unstable aberrations include dicentric and multicentric chromosomes, centric and acentric rings, "double minutes," and acentric fragments. Stable aberrations include inversions and translocations. Because stable aberrations were graded from large and obvious to small and subtle, the observations on stable aberrations are not as reliable as those on unstable aberrations. On the other hand, since all observations were

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Table 1. Results of cytogenetic analysis of culture lymphocytes from 48 residents of the former Soviet Union

Characteristic	Control population		Contaminated population	
	Number*	Cells†, no.	Number*	Cells†, no.
Unstable aberration				
Dicentrics	21	16	19	19
Tetracentrics	2	2	0	0
Rings	2	2	5	5
Acentric rings	4	4	6	6
Minutes	10	8	6	6
Acentric fragments	18	17	21	21
Stable aberration				
Trans + Inv	16	16	18	18
Type of cell				
Cu		42		45
Cs		15		15
Rogue		9		0
Normal		4714		4657
Total cells observed, no.		4780		4717

For the control population, 24 subjects (20 men and 4 women) were studied and, for the contaminated population, 24 subjects (11 men and 13 women) were studied. Trans, translocations; Inv, inversions; Cu, cells with unstable chromosome aberrations; Cs, cells with stable chromosome aberrations (when cells contain both unstable and stable aberrations, they are classified as Cu cells).
*Number refers to the number of chromosome aberrations observed.
†Cells containing the aberration or with the indicated characteristic.

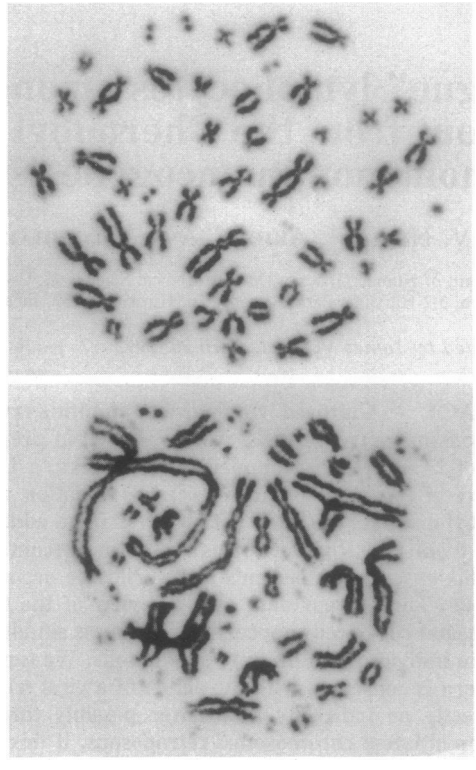

FIG. 1. Two rogue cells from Ukrainians, selected to illustrate the extreme in the damage encountered.

made in the same laboratory on slides coded as to exposure status, there should be no bias in the observations on stable aberrations.

The striking finding is the occurrence of one or more rogue cells in the samples from eight persons, all from the control village of Krasilovka. Two of these rogue cells, selected to illustrate the extremes in the damage encountered, are shown in Fig. 1. In this control population, 9 rogue cells were observed among the 4780 cells scored (0.19%), a frequency of 1 rogue cell per 531 cells examined. (Because the population distribution of rogue cells is unknown, we will not attach sampling errors to these percentages.) Two aspects of these cells are especially noteworthy—namely, the relatively high proportion of chromosomes with two or more centromeric constrictions and the frequency of small paired acentric fragments of various sizes (double minutes). For cells exhibiting simple chromosomal damage, when rogue cells are excluded, the frequency does not differ significantly in the Krasilovka and Novozybkov–Zlynka populations, for cells with unstable or stable aberrations, although there is slightly more damage in the more contaminated group. The cytogenetic effects of the radioactive contamination from Chernobyl will be combined with other data and the results will be presented at a later date by the International Atomic Energy Authority.

An obvious question is whether the frequency of cells with simple damage is elevated in individuals with rogue cells. In the 8 persons with rogue cells, the frequency of cells with unstable simple damage is 1.01% and the frequency of stable simple damage is 0.51% (total scored, 1580 cells) whereas, in the 16 persons not exhibiting rogue cells, the corresponding figures were 0.81% and 0.22%, respectively (total scored, 3200 cells). The differences are small but in the direction to be expected if the process resulting in rogue cells was also increasing the number of cells with simple damage.

Table 2 presents some details on the detection of rogue cells. One of the best descriptors of a rogue cell is the number of double minute fragments present in the cell. In extreme cases, an accurate count of the number of these fragments is difficult, and the number is simply indicated as >10 or >20. Six of the 9 rogue cells fall into the >10 category. The damage in these cells is of a complexity seldom seen in cells that were viable and able to initiate mitosis at the time of collection. The average age of the persons in whom rogue cells were detected in Krasilovka was 45.4 ± 10.6 years whereas the average age of those in whom they were not detected was 46.2 ± 9.5 years. (The excess of persons whose ages terminated in a zero is the result of the population sampling strategy.) With respect to sex, in Krasilovka, 6 of the 8 persons exhibiting rogue cells were males, whereas 15 of the 17 persons in whom rogue cells were not detected were males.

All of the individuals who were karyotyped had completed the personal and medical questionnaires (58 items) and had undergone the standardized physical examination (19 items) and the complete blood count that was characteristic of the Chernobyl medical follow-up studies (cf. pages 291–294 of ref. 7). Since, however, there was an unavoidable element of self-selection in the composition of the sample (7) and the widespread fear of the effects of fall-out from the Chernobyl

Table 2. Some details concerning the characteristics of rogue cells

Patient	I.D. no.	Sex	Age, years	Double minutes, no.
P572	05975	M	40	>30
				6
RP573	06190	M	42	5
RP575	06009	M	40	>20
RP581	06246	F	46	>10
RP584	05924	F	60	>10
RP587	06262	M	29	5
RP588	06106	M	40	>20
RP591	05967	M	60	>20

I.D., identification; M, male; F, female.

disaster even in uncontaminated regions undoubtedly colored medical histories, we will restrict this analysis to the hematological findings, which should be the most objective. Two analyses have been conducted: one contrasting the findings in Krasilovka with those in Novozybkov and Zlynka and the other contrasting the findings in Krasilovka of those in whom a rogue cell was encountered with those in whom a rogue cell was not encountered. Small though the numbers are, to our knowledge, this is the first opportunity to search in a systematic way for concomitants of the rogue-cell phenomenon. With respect to the erythrocyte parameters (erythrocyte cell count, hemoglobin, and hematocrit), there were no differences between the three towns nor, in Krasilovka, between those with and without rogue cells nor were there any differences with regard to platelet counts. With respect to the leukocyte studies, within Krasilovka, there was no difference between those with and without rogue cells but, when the pooled sample was compared with the results from inhabitants of the two contaminated villages, significant differences emerged. Total leukocyte counts did not differ (Krasilovka, 8045 cells per mm^3 vs. Novozybkov–Zlynka, 7750 cells per mm^3) but, in Krasilovka, there was a relative lymphocytopenia (35.0% vs. 42.7%; $P = 0.0056$) accompanied by a relative excess of segmented polymorphonuclear leukocytes (55.8% vs. 48.1%; $P = 0.0064$) and also an excess of monocytes (6.1% vs. 3.4%; $P = 0.0003$). It is tempting to speculate that this lymphocytopenia reflects a recent viral infection of some of the residents of Krasilovka.

DISCUSSION

We will confine our discussion to the observations on rogue cells. It is now apparent that their occurrence is a worldwide phenomenon, the cells having been observed among cultured lymphocytes from the Yanomama Amerindians of Venezuela (1), from Japanese residing in Hiroshima and Nagasaki who were not exposed to the atomic bomb explosions (4), from Englishmen (2, 3), and from Ukrainians (this paper). There are also anecdotal observations of their occurrence in the United States (8), Japan (M. S. Sasaki, personal communication), and China (J. Cuizhen, personal communication). The following aspects of the accumulating data concerning rogue cells are noteworthy.

Cytology of Rogue Cells. As noted earlier, the number of double minute fragments in a rogue cell is a convenient indicator of the degree of damage, although for technical reasons, all double minute counts must be regarded as a minimum. Table 3 summarizes the occurrence of double minute fragments in the three populations studied by ourselves. Note that even in this limited sample of 44 rogue cells, there are several exhibiting as few as two or three double minutes. A typical rogue cell presents an unforgettable picture. The range of variation documented in Table 3, however, raises the question of the lower limits of damage consistent with the appellation. In karyotyping, single cells are sometimes encountered with evidence of multichromosomal damage, such as a translocation, a dicentric, and a fragment. On the basis of admittedly limited data, we suggest that the spectrum of chromosomal damage in rogue cells follows a more-or-less normal frequency distribution and that, with respect to the lower limits of this distribution, there is no clear dividing line between rogue cells and cells not given this designation that have evidence of multichromosomal damage.

Table 3. Occurrence of double minutes in rogue cells from three populations

Population	Rogue cells examined, no.	Cells with the indicated double minutes, no.					
		2–3	4–5	6–7	8–9	>10	>20
Amerindian	11	1	4*	2†	2	1‡	1‡
Japanese	24	4	6§	3¶	—	11	—
Ukrainian	9	—	2	1	—	2	4
Total	44	5	12	6	2	14	5

*Includes one 5-or-more double minute fragment.
†Includes one 6-or-more double minute fragment.
‡Tetraploid cell.
§Includes one >4 double minute fragment.
¶Includes one >7 double minute fragment.

The rogue cells pictured in Fig. 1 would not survive a mitotic division. Indeed, even among less-damaged cells, a single dicentric may be incompatible with the long-term survival of the progeny of that cell. However, the same event of two chromosomal breaks which leads to a dicentric and a free fragment, in principle has an equal probability of resulting in a reciprocal translocation or, if both breaks occur in a single chromosome, an inversion; these latter events should result in stable or quasistable chromosome abnormalities. We suggest that the process that gives rise to a typical rogue cell may occasionally result in cells with lesser degrees of damage, consistent with cell multiplication.

Association of the Occurrence of Rogue Cells in Populations and/or Individuals with an Increase in "Simple" Chromosome Damage in the Same Population and/or Individual. For present purposes we define "simple" chromosomal damage to include multicentric chromosomes, double minutes, free fragments, centric and acentric rings, translocations, and inversions. Three lines of evidence suggest that the frequency of simple chromosomal damage is increased in nonrogue cells in the presence of the rogue-cell phenomenon. (*i*) In the original Yanomama data (1), 0.43% (21 in 4875 cells) of the cultured cells showed simple damage of the types enumerated, whereas in studies in the same village 2 years later, when the frequency of rogue cells had subsided to 0.01% (1 in 9849 cells), the corresponding percentage was 0.28% (28 in 9849 cells) (9). (*ii*) In the observations of Tawn *et al.* (3), the frequency of cells exhibiting simple unstable chromosome damage in the two individuals exhibiting rogue cells was 1.5% (15 of 1000 cells), whereas in the 10 individuals not exhibiting such cells the frequency was 0.2% (4 in 2000 cells). (*iii*) As described earlier, among the 8 persons exhibiting rogue cells in a Ukrainian village, the frequency of cells with unstable simple damage was 1.01% and the frequency of stable simple damage was 0.51% (1580 cells scored) whereas, in the 16 persons not exhibiting rogue cells, the corresponding figures were 0.81% and 0.22%, respectively (3200 cells scored). None of these differences is statistically significant, but all are in the direction to be expected if the process leading to rogue-cell formation was also contributing cells with lesser damage to the population of circulating lymphocytes.

Nonrandomness of the Rogue-Cell Phenomenon Among Individuals. That the rogue-cell phenomenon is nonrandomly distributed among individuals seems clear. In the study of Japanese subjects, among the 24 persons exhibiting rogue cells, only one such cell was observed among the 10 cells routinely scored for each individual. The overall frequency of rogue cells in the Japanese population was 0.02% (24 in 102,170 cells scored). For each of those individuals exhibiting a rogue cell, as many additional cells as the preparations permitted were scored beyond the original 10 cells. Among 2138 cells so scored, 7 rogue cells were observed. This frequency (0.33%) is very significantly higher than the frequency in the total sample ($\chi^2 = 65.1$; degrees of freedom = 1; $P < 0.001$) (4). The data of Tawn *et al.* (3) also appear to establish a dichotomy between persons exhibiting these cells and persons in whom they are absent or present at a much lower frequency. But while the phenomenon is nonrandomly distributed among individuals, it has not yet been established whether only certain individuals are susceptible to the phe-

nomenon or whether susceptible persons will experience repeated bursts of these cells.

Distribution of the Rogue Cells by Geography. The evidence is clear that at any given time the rogue-cell phenomenon has a patchy geographical distribution, affecting multiple individuals in some localities but being apparently absent or at low frequencies in other areas in the same region. In the same round of fieldwork in which 0.45% (23 in 5165 cells) of the cultured lymphocytes of residents of two adjacent Venezuelan villages of Yanomama were found to be rogue cells, none of 2660 cultured lymphocytes from blood samples from the Piaroa, another Venezuelan tribe some 170 km west, was found to be a rogue cell (9). Likewise, as noted earlier, at the same time we encountered 0.19% rogue cells in cultured lymphocytes from the Ukrainian village of Krasilovka, no such cells were encountered in two Russian villages some 200 km north–northeast. In samples collected in adjacent Byelorussia at about the same time, A. V. Sevankaev, A. F. Tsyb, A. A. Zhloba, V. V. Moiseenko, A. M. Skrjabin, V. M. Klimov, and D. Lloyd (personal communication) observed 1 rogue cell in ≈7800 cells scored from 39 controls and 7 rogue cells in ≈32,200 cells from 161 children who were evacuated from the area contaminated by the Chernobyl disaster about 1 week after the accident. The difference between the two Byelorussian groups is negligible and in the combined data the frequency is ≈0.02% (1 in 5000 cells), quite similar to that observed in the later Amerindian data and the Japanese study.

Distribution of the Rogue-Cell Phenomenon in Time. The transient nature of the rogue-cell phenomenon in individuals is best illustrated by the findings of Tawn *et al.* (3): two individuals in whom 0.9% of 1000 cells were rogues exhibited no cells of this type when another 1000 cells were examined 50 days later. The transient nature of the phenomenon for populations is best illustrated by the finding of only 0.01% rogue cells (1 in 9849 cells) in two Yanomama villages in which, 2 years earlier, the frequency had been 0.43% (9).

Further Epidemiologic Facts. In the studies in Japan, the mean age was 24.55 ± 6.2 years in those exhibiting rogue cells and was 23.4 ± 6.2 years in those in whom rogue cells were not observed (4). In the present studies in the Ukraine, the mean age was 45.4 ± 10.6 years in those with rogue cells and was 46.2 ± 9.5 years in those without rogue cells. The difference in age between the Japanese and the Ukrainians results from the nature of the populations studied. The age similarity between those with and without rogue cells does not suggest that the appearance of rogue cells is triggered by a "childhood" disease. In neither of these two instances did the sex ratio among those in whom rogue cells were detected differ from that of the total sample.

Numbers of Rogue Lymphocytes in Circulation. The frequency of rogue cells at the height of a "burst" or "wave" is unknown. In the data of Tawn *et al.* (3), for the two individuals concerned, the initial frequencies were 1 in 125 cells and 1 in 100 cells. In the two Amerindian villages in which the phenomenon was first encountered (1), the frequency was 1 in 233 cells, but there was marked heterogeneity in the data. The average ("baseline") frequency of these cells in the second sampling of Amerindians and in the Japanese and Byelorussian material was ≈1 in 5000 lymphocytes. Although, because of the unknown distribution of rogue cells in time and individuals, it may be misleading to base any precise calculation on this average, the numerical implications of the data are intriguing. Even at the low population "baseline" frequency of 1 in 5000 cells, the total number of rogue cells in circulation in an adult, assuming all lymphocytes exhibit the same frequency as the T cells that proliferate in culture, calculated as lymphocytes per mm^3 of blood × blood volume in mm^3 × rogue-cell frequency, should be approximately $(2.5 \times 10^3) \cdot (5 \times 10^6) \cdot (2 \times 10^{-4}) = 2.5 \times 10^6$. At the height of a burst in the frequency of such cells, when they may constitute 1 in 100 lymphocytes, the total number in circulation could be 1.3×10^8 cells. If only 1 in 1000 of these cells is characterized by cytogenetic rearrangements compatible with cell division, the number of rogue cells in circulation capable of replication becomes in the latter situation 1.3×10^5 cells.

Cause(s) of This Phenomenon. The foregoing facts set the stage for certain speculations concerning the etiology and biomedical significance of the rogue-cell phenomenon. The circumstances of the discovery of the phenomenon, in Amerindians living in a tropical rain forest, prompted the speculation of a viral etiology (ref. 1; see also ref. 4). That such viral infections as measles, mumps, and chicken pox can induce an increase in chromosome damage *in vivo* was established some 30 years ago (10–12), and by the 1970s, there was an extensive literature on the effect on chromosomes of these and other viruses *in vivo* and *in vitro* (for reviews, see refs. 13–15). In contrast to the present findings, however, at the height of the viral infection, simple chromosomal damage was often increased 4- to 5-fold, no rogue cells were observed, and Nichols (ref. 16, p. 449) has pointed out that "in the acute stage the virus-induced defects were of the open type with little reunion occurring." With the virus multiplicities achieved *in vitro*, the damage is often characterized by chromosomal pulverization, although Moorhead (13) pictures a typical rogue cell in a WI-38 human cell line infected with mycoplasma and Nichols *et al.* (17) observed a similar cell in a simian virus 40-infected human diploid fibroblast line.

Damage to specific lymphocytes from contact with the radiation of an ingested α-emitting particle must also be considered as an explanation, but the failure to observe rogue cells in individuals with an increased body burden of such particles, such as workers with exposures to plutonium (18–20), mitigates against that conclusion. We have seen rogue cells in individuals receiving repeated doses of therapeutic radiation to the pelvic region (A.A.A., unpublished data), but the radiation doses involved far exceed those which might be experienced by the populations exhibiting rogue cells. In the present study, the absence of rogue cells in two villages where fall-out from Chernobyl was greater than in Krasilovka (as well as the results of studies in which radiation is not implicated) strongly militate against this being a radiation effect. Hsu (8) speculated that the single rogue cell he observed might be due to "a defective DNA synthesis system, probably as the result of a mutation," but the subsequent developments would require an extraordinarily high somatic cell mutation rate if this is to be considered a general explanation. Ahuja (21) suggests the cells might result from an invasive bacterial species that then releases restriction endonucleases.

Our recent data from the Soviet Republics again force us to consider an infectious etiology, with, by elimination, the most likely candidate appearing to be a virus or viruses. (We note in retrospect that although in the work among Amerindians we traveled as a medical team and often provided therapy to Indians who were ill, we were not made aware of any unusual pattern of recent or current illness among the residents of the two Amerindian villages in which rogue cells were first encountered.) Whereas, however, the original observations permitted the postulate of a virus endemic to the tropical rain forest (in consequence of which its effects had not previously been observed by the cytogenetic community), now the epidemiologic facts demand that the viral trigger(s), if virus it be, are of very wide distribution. Furthermore, the age distribution of those exhibiting rogue cells suggests that the postulated viral infection is not a once-in-a-lifetime affair but an infection that does not confer lasting immunity.

The viral infection we are postulating may in some unknown fashion be directly responsible for the chromosomal damage of the rogue cells, for example, as through the release of a

transposase by a retrovirus, a transposase that could activate some specific subset of the transposon–retroposon-like sequences known to be so numerous in the human genome, with this activation being responsible for the chromosomal damage. An alternative suggestion—resulting in a two-step hypothesis—is that the infection simply activates latent retroposons, which then produce the observed chromosomal damage. This postulate, of retroposon–transposon activation, is prompted by the fact of the apparent difference in the nature of the chromosomal damage observed in individuals exhibiting rogue cells and the damage observed *in vivo* at the height of measles, mumps, and chicken pox infections.

The literature on the characteristics of retroposon–transposon systems, in *Escherichia coli*, maize, and *Drosophila*, is enormous, and no attempt to review it can be made in this communication. We simply suggest at this time that the observations on rogue cells fit well into the framework of knowledge concerning these systems and meet the expectations created by the presence of 1×10^6 retroviral-related sequences of various types in the human genome. Evidence that in humans some of these are mobile and, hence, must be associated with chromosome breakage and reunion is just now becoming available (22–25).

Possible Biomedical Significance of the Findings. The biomedical significance of the rogue-cell phenomenon in the broad sense depends on its tissue distribution. At present, the rogue-cell phenomenon in humans has only been established in lymphocytes, where the resulting chromosomal rearrangements and losses that are transmissible, cell-viable, and involve the appropriate genes may initiate the oncogenic process. The more general thesis, as we have suggested (4), is that the phenomenon occurs in a variety of tissues, each of which may differentially express the damage. Thus, if the phenomenon occurs in other somatic tissues, then the resulting transmissible chromosomal rearrangements or deletions may play a role in initiating or facilitating the oncogenic process in these tissues, the precise type of cancer being specific to the chromosomal breakpoint and tissue. If the phenomenon occurs in the germ line, then the transmissible unbalanced genomes would form the basis for some fraction of the children with congenital malformations, and the balanced genomic rearrangements that are transmitted would play a role in mutation and the chromosomal rearrangements of evolution. This thesis may be regarded as an extension of an earlier viewpoint emphasized by Nichols (16, 26) concerning the role of transmissible viruses in inducing chromosomal damage and resulting in oncogenesis, teratogenesis, and mutagenesis—an extension now possible because of the demonstration of the ubiquity of retroposon sequences in the human genome and the epidemiological evidence summarized in this paper. However, we especially note the lack of an age correlation in our data, which suggests that unlike the viral diseases of childhood, the infectious trigger may be repetitive.

Speculation concerning a major role of transposons (and the related "mutator" genes) in mutation, cancer, and evolution has been frequent in recent years (e.g., refs. 27–32). Even so, at present, the human chromosomal rearrangements involved in oncogenesis or responsible for a congenital defect still are generally viewed as primarily stochastic in nature, inherent in the complexity of the genetic material. If rogue cells are in fact ubiquitous evidence for the periodic activation of chromosomal retroposons, with the consequences we have suggested, these chromosomal events, instead, may be to some considerable extent process-driven. The bursts in which rogue cells occur, both in individuals and in populations, require, under the present hypothesis, some process-initiating (retroposon-activating) event that could result in the mutator phenotype postulated by Loeb (33) as responsible for multistage carcinogenesis. Thus far evidence for an exogenous viral infection activating latent mammalian retroposon systems seems to be lacking but now must be sought. It is a legitimate speculation that transmission/activation of the viral agent we postulate may in time be shown to be amenable to at least partial control, albeit such control will be more complex than that achieved for measles, mumps, and chicken pox, other clastogenic agents. The implications of control of the more extreme rogue-cell phenomenon for decreasing the frequency of congenital defect and cancer might be considerable. At the moment, there is no more promising lead in sight to a reduction in the frequency of these diseases at the primary level.

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