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CYTOGENETICAL STUDIES ON A LARGE CONTROL POPULATION AND ON PERSONS OCCUPATIONALLY EXPOSED TO RADIATION AND/OR TO CHEMICALS

S. GUNDY

Department of Human Genetics and Teratology, National Institute of Hygiene, Budapest, Hungary

Summary. - *Nowaday all people are exposed to mutagens environmentally, occupationally, therapeutically or due to the life style. In order to validate any conclusions concerning a possible effect of some kind of these mutagens to the relevant exposed groups, chromosomal analysis was carried out on a standard population (211 persons) distributed randomly from biological and social points of view and on 163 persons, occupationally exposed to different kinds of mutagens. Analysis proved that the mean frequency of chromosomal aberrations (CA) of control was 0.81% and it was similar before and following the Chernobyl events. Data concerning the CA frequency in people exposed occupationally to low doses of ionizing radiations below the internationally accepted permissable level, showed a 2-6-fold increase of aberrant cells. Occupational exposure to chemical mutagens such as vinylchloride and organic solvents like benzene and toluene revealed 2-4 times higher frequency of CAs than the control; however, exposures to organophorus insecticides reached a 5-6-fold increase in CAs as well. The sister chromatid exchange (SCE) frequency data were in each exposed group higher than the control values. Neither chromosomal aberration frequencies, nor sister chromatid exchanges differed significantly between smokers and non smokers in control and exposed persons.*

Riassunto (Studi citogeneciti su un'ampia popolazione di controllo e su persone esposte occupazionalmente a radiazioni e/o sostanze chimiche). - *L'intera popolazione è oggi esposta a mutageni di origine ambientale, occupazionale, terapeutica o dovuti allo stile di vita. Per analizzare gli effetti di alcuni di questi mutageni su gruppi esposti di particolare interesse, sono state fatte analisi cromosomiche su di una popolazione di controllo (211 persone) assortita a caso riguardo a fattori biologici e sociali, e una popolazione di 163 persone esposta per ragioni occupazionali. La frequenza media di aberrazioni cromosomiche nei controlli era 0,81%, ed era simile sia prima che dopo gli eventi di Chernobyl. La frequenza di aberrazioni cromosomiche nelle persone esposte a basse dosi di radiazioni ionizzanti (sotto i livelli internazionalmente accettati) aveva un aumento da 2 a 6 volte. L'esposizione occupazionale alle sostanze cloruro di vinile, benzene e toluene provocava un aumento da 2 a 4 volte della frequenza di aberrazioni cromosomiche. Invece l'esposizione a insetticidi organo-fosforici faceva aumentare le aberrazioni di 5 o 6 volte. Le frequenze di SCE rispetto ai controlli erano più alte in ognuno dei gruppi esposti. Non c'era differenza significativa né di aberrazioni cromosomiche né di SCE tra i fumatori e i non fumatori sia dei controlli che degli esposti.*

Introduction

Most physical and chemical agents that break chromosomes and produce structural chromosomal changes called clastogens, are also mutagens and *vice versa*.

All appear to damage DNA in one way or another, and the type and frequency of chromosomal aberrations (CA) or manifestation of sister chromatid exchanges (SCE) will differ depending upon the agent caused them, in a given phase of the cell cycle.

Unfortunately, there are relatively few methods to measure or to indicate damages in mutagen exposed human cells, but the analysis of chromosomal breaks and rearrangements, or the detection of the frequency of sister chromatid exchanges seem to be useful tools in the evaluation of potential hazards of mutagens and carcinogens.

For many years the ionizing radiations have been the subject of interest and of most studies. It was not surprising, since it was the first man-made agent that was shown to be mutagenic and carcinogenic. In the development of cytogenetics, the necessary techniques became available in the late 1950's and it was quickly shown that chromosomal aberrations in peripheral blood lymphocytes of exposed persons might be successfully applied not only as biological indicators of the mutagenic effect, but also as a dosimeter for the estimation of absorbed radiation dose in man [1]. The reliability of biological dosimeter can be influenced by different factors, however, a reasonable dose estimation can be made on individual level especially at acute, single exposures. Beside this we are also able to estimate increased genetic or carcinogenic risk from

population data. The possible estimation of ill-health is also feasible on population, because of the fact that the dose distribution is determined by physical factors rather than biological ones.

We have such an example on Hiroshima and Nagasaki population exposed to ionizing radiations as to a powerful mutagen and carcinogen, displaying a strong cytogenetical evidence of the exposure many years later [2]. Besides indication of mutagenic effect it is possible to describe the shape of dose-effect relationships on the base of chromosomal damages [3, 4] and clearly a greater cancer risk than in unexposed population [5].

On the health of the offspring of these people, however, genetic studies have failed to demonstrate any effect [6, 7].

In the face of multiplicity of possible chemical mutagens and carcinogens to which people might be exposed, we have more confusing cytogenetical information. On the basis of empirical data it is indicated, that chemical mutagens are able to induce both, true gene and chromosome mutations (SCE as well), whilst ionizing radiation induces predominantly chromosomal aberrations [8]. Chromosomal aberrations are, however, not believed to constitute the major class of mutations that can be expected to give rise to the cancer risk or genetic ill-health, at the same time they must indicate some parallel induction of other classes of mutations occuring in different cells of organism.

The use of CA and SCE analysis as a method of biological dose estimation for chemicals is virtually impossible. The assay is more applicable to individuals. The dose estimation is complicated, because the exposure to chemicals is largely influenced by biological factors and most of the chemical agents act on the cell and cellular DNA in different way than the ionizing radiations. Even if we know a lot about the chemical properties of the mutagen, the kind of lesions produced in the DNA will differ and we still require to know more about the spectrum of its genetic effects and consequences.

In order to infer risk from chemicals we have an indicator of exposure which responds to mutagens or carcinogens in the face of increased CA or more often of SCE frequencies. Concerning ill-health of future generations, we have less information about chemical mutagens than about the radiation: therefore to determine the relative frequency of chromosomal *versus* gene mutations in chemically exposed people is one of our most important tasks. If we compare cytogenetic effects of radiations and chemicals on individuals, a serious problem seems to be arised by the greater heterogenity in mutagenic response to chemicals than to radiation, which can vary quite widely between different people. How many variations exist, we do not know, therefore each chemical mutagen must be considered in its own right.

One of the next problems we have to clarify, is the question of the persistence of chromosomal aberrations, following chemical exposure *in vivo*. It is well known, that stable chromosome rearrengements following irradiation persist for many years, but this has not been shown to occur after chemicals.

In the present work we attempted to make comparison between groups, occupationally exposed to different radiation sources and/or to chemicals under the same experimental conditions.

In vivo studies with radiations, particularly for dose estimation studies have largely been concerned with individuals or populations, exposed to relatively high doses, and we have only few data on occupationally exposed workers where the levels of irradiation were below the maximum permissable level of 50 mSv *per annum* [9, 10]. With chemicals we have just the opposit, i.e. there are almost no information concerning acute, large doses of exposures, except some accidents like those of Bhopal [11], but the studies on occupationally exposed groups are coming also from different laboratories, with different experimental conditions, giving problems for correct comparison, and final conclusions.

Our cytogenetical monitoring attempts to find "high risk" occupations among selected Hungarian workplaces taking into consideration that we are in need of more and more data on man, therefore we have to include all kind of information received on man himself.

Materials and methods

Subjects

Blood samples for the analysis of structural chromosome aberrations and sister chromatic exchanges were collected by venipuncture. All subjects were interviewed about recent viral infections, diagnostic or therapeutical irradiation, drug intake, alcohol consumption and smoking habits. Blood samples from exposed and control individuals were processed concurrently. No differences in this respect could be found between the workers and controls. Occupational exposure had not caused clinical symptoms in the workers and all controls also informed to be healthy and they were not in contact with those agents as exposed people, and most of them were new employment recruits, soldiers, clerks, students, salesmen, etc. Thirty-six persons among controls were separately investigated after Chernobyl events, for the correct evaluation of "back-ground" aberration and SCE levels. SCE analysis was carried out on 76 of 211 control persons, comprising on 40 people before and 36 people after Chernobyl events. Smoking habits were statistically analyzed only in such 3 groups, where the aberration rate was the smallest and where a sufficient number of individuals could be found. These data were gathered only after completion of the study. Further data of people examined are presented in Table 1. All persons were living or working in the same geographic area and controls included the worksite controls as well. Altogether 211 controls and 163 exposed persons were tested cytogenetically and the exposed people were categorized into various groups as indicated in Table 1. "Radiation" groups (II and III) handling unsealed radiation sources like ^{3}H, ^{14}C, ^{32}P, ^{59}Fe, ^{131}I and ^{125}I worked with organic and anorganic solvents.

Table 1. - *Data of persons occupationally exposed to different kinds of mutagens*

Groups		no. of persons	Age	Duration of exposure (years) mean	range
I	Controls	211	36.1	-	-
II	Personnel of research laboratories using isotope labeled compounds in Ci and mCi activities	28	35.6	10.8	1-27
III	Workers producing isotopes in mCi and Ci activities	21	44.1	15.5	8-21
IV	Persons handling X-ray and gamma-ray apparatuses	13	42.6	15.6	3-23
V	People working at neutron generator, in physical research field	13	36.4	13.8	1-24
VI	Persons working in chemical research laboratories using organic and anorganic solvents	17	36.7	15.2	5-22
VII	Factory workers producing organophosphorus insecticides	24	29.2	6.8	1-23
VIII	Factory workers producing poly-vinyl-chloride	37	36.1	13.1	1-25
IX	Factory workers using toluene and benzene	10	39.5	11.4	1-27

Film-badge and personal dosimeter data of groups II-V never showed larger exposures than the accepted Hungarian occupational limit of 50 mSv *per annum*, so numerical cumulative dose estimates are not indicated. In "chemical" groups measurements have been made wherever it was possible. Personal exposure to vinyl-chloride from 0.1-15.8 mg/m³ air was found (the average 4.66 mg/m³) and the toluene and benzene from 6.8-33.8 mg/m³ (the average 25.5 mg/m³) for 8 h workperiod.

Air concentrations for organophosphorus insecticide production were not available.

Cell culture and chromosome analysis

The samples of blood for chromosome analysis were coded before being set up in 48 h cultures. The lymphocytes were cultured in TC-199 medium with autologous plasma as described earlier [12]. One hundred cells per person (except in group VII at 2 persons) were scored as recommended by WHO [13] and all terminal and interstitial deletions and isochromatid deletions in the absence of sister union were recorded as acentric elements. The cells were analyzed independently by three persons.

For the SCE analysis a modification [14] of Perry and Wolff's method [15] was used. Only spreads with from 44 to 47 centromers were included in the totals and centrometric and distal sister chromatid exchanges were scored in 50 cells of each person.

Statistical procedures

Aberration levels for each group were analyzed as number and the percentage of the type of aberrations found in 100 cells, and as distribution of aberrations determined in control and occupationally exposed groups, which were distributed into two larger categories such as "radiation" and "chemically" exposed ones.

Statistical comparisons were made using χ^2 tests.

Results and discussion

Table 2 displays in detail the types and frequencies of chromosomal aberrations in controls and in different exposed groups.

Chromatid breaks, acentric fragments, dicentrics and centric rings were recorded. We identified only 2 chromatid exchanges in group VII, therefore we did not indicate them separately.

Table 2. - *Type and frequency of chromosomal aberrations and SCEs in controls and in different occupational categories*

Groups	no. of cells examined	Chromatid deletions		Acentric fragments		Dicentrics (rings)		Total		SCE cell ± S.D.	Range of SCE
		no.	(%)	no.	(%)	no.	(%)	no.	(%)		
Control	21,100	90	0.43	69	0.33	12	0.05	171	0.81	5.55 ± 0.65*	4.49-7.64
After Chernobyl only	(3600)	(12)	(0.33)	(7)	(0.19)	-	-	(19)	(0.53)	(5.58 ± 0.65)	(4.64-7.52)
II	2800	18	0.64	19	0.68	8	0.29	45	1.61	7.39 ± 1.30	4.88-10.11
III	2100	62	2.95	68	3.24	8	0.39	138	6.57	7.68 ± 1.73	5.15-13.92
IV	1300	13	1.00	8	0.62	12	0.92	33	2.54	8.46 ± 0.94	7.13-10.06
V	1300	37	2.85	32	2.46	8	0.62	77	5.92	7.43 ± 1.33	5.48-9.67
VI	1700	8	0.47	10	0.59	-	-	18	1.06	6.16 ± 0.77	5.14-7.18
VII	2066	101	4.89	13	0.63	3	0.15	117	5.66	9.56 ± 2.11	5.42-13.66
VIII	3700	48	1.30	11	0.30	5	0.14	64	1.73	7.52 ± 1.31	5.30-10.52
IX	1000	25	2.50	8	0.80	1	0.10	34	3.40	8.48 ± 1.28	7.28-11.00
Exposed to radiation (II-V)	7500	130	1.73	127	1.69	36	0.48	239	3.91	7.74 ± 1.33	4.88-13.92
Exposed to chemicals (VI-IX)	8466	182	2.15	42	0.50	9	0.11	233	2.75	7.93 ± 1.37	5.14-13.66

(*) 3800 cells from 76 persons were examined

The results of χ^2 test showed inhomogeneity in the distribution of chromosomal aberrations with respect to different working groups. According to the more detailed analysis it could be explained due to aberrations observed in groups III, V and VII.

Percent values of all the types of aberrations were consequently higher in exposed groups than in the controls.

Comparing groups separately, we found that the higest frequency of chromatid deletions appeared in exposed persons of group VII who produced organophosphorus insecticides. Results reported in the literature are not conclusive so far in this respect. Van Bao *et al.* [16] and Dulout *et al.* [17] found increased chromatid breaks in these occupational groups, however others, as Högstedt *et al.* [18] and Stocco *et al.* [19] did not detect an increased level of chromosomal aberrations in pesticide workers. Since the use of pesticides varies a great deal between different countries and we have data not on users but on factory workers producing unequivocally organophosphate pesticides, we found wortwhile to study this group.

The maximum level of dicentrics occured in people, handling external radiation sources in group IV. It is of course not surprising, because the exchange type aberrations are mainly present in radiation exposed people, as indicators of radiation exposure [1]. At the same time the role of organic and anorganic solvents might not be excluded in the production of chromatid deletions, in group III.

Chemicals induce mostly chromatid type aberrations but the extent of these breaks and their relative proportion to other aberrations can vary in a wide range in chemically exposed people. Therefore the study of human specimen (where chemicals and ionizing radiations are acting simultaneously) can give useful information, in "mixed exposure" categories. In this study we found relatively low frequency of chromosomal aberrations in workers producing poly-vinyl-chloride (PVC). The importance of the study of PVC effects is connected with its association with human cancer which was first published in 1974 [20]. The percentage of chromosomal aberrations was also highly elevated in this occupational group [21, 22]. Our investigation were carried out more recently, therefore the low percentage of aberrations was probably occurred due to use of small concentrations of vinyl-chloride in the working zones.

Benzene itself does not influence cytogenetical changes in cells [23] exposed *in vitro*. However, in our *in vivo* investigations significantly higher aberration and SCE rate was demonstrated in group VIII than in controls, which indicates that the metabolites of benzene are rather clastogonic than the benzene itself.

Comparing to the control, all SCE data revealed significantly higher values in different exposure categories. The widest range of SCEs was found in groups III and VII. It is usually accepted, that SCEs are not elevated as the effect of ionizing radiations: however, we found higher frequency in each "radiation" group than in controls, even in persons not contacting with chemical solvents. Because cytogenetic endpoints in peripheral lymphocytes are often used to monitor DNA damaging agents, this fact is an important one, which was already established preliminarly in one of our previous work [14].

The yield of chromosomal aberrations and SCEs found in controls after Chernobyl events are also presented in Tables 2 and 3. These data are shown separately, in order

Table 3. - *Sister chromatid exchanges frequency in control persons before and after Chernobyl events*

	Total	Males	Females	Before Chernobyl	After Chernobyl
no. of persons	76	39	37	40	36
no. of cells examined	3800	1950	1850	2000	1600
SCE/cell ± SD	5.55 ± 0.65	5.48 ± 0.62	5.62 ± 0.69	5.51 ± 0.63	5.58 ± 0.68
range of SCE	4.49 - 7.64	4.49 - 7.64	4.94 - 7.52	4.49 - 7.64	4.64 - 7.52

Table 4. - *Distribution of aberrations in controls and in occupationally exposed persons*

Aberrations (%)	Controls		Persons occupationally exposed to radiation		Persons occupationally exposed to chemicals	
	no.	(%)	no.	(%)	no.	(%)
0	139	65.9	10	13.3	21	23.9
1	20	9.5	14	18.7	17	19.3
2	26	12.3	7	9.3	19	21.6
3	12	5.7	13	17.3	10	11.4
4	8	3.8	7	9.3	8	9.1
5	5	2.4	3	4.0	3	3.4
6	1	0.5	7	9.3	2	2.4
7			6	8.0	2	2.3
8			2	2.7	1	1.1
9			1	1.3	1	1.1
10			1	1.3	1	1.1
11			0	0.0	1	1.1
12			1	1.3	1	1.1
13			0	0.0	1	1.1
14			1	1.3		
-			-	-		
-			-	-		
-			-	-		
18			1	1.3		
19			0	0.0		
20			1	1.3		
Total	211	100 (*)	75	100 (*)	88	100 (*)

(*) percents were rounded to the nearest whole number

to underline, that a two-three fold elevation of the radiation dose-level in Hungary during the first weeks after Chernobyl accident [24] and the consequencies of food contamination caused neither in chromosomal nor in SCE yields cytogenetical changes in our control. These data are completely compatible with our previous control data, thus they can serve as a part of historical control values.

Table 4 gives an insight into the character of distribution of aberrations in controls and in two large exposed categories. A wide scale and variety of persons carries more than 1% of chromosomal aberrations in all groups. In our study we also tried to establish the role of some confounding factors influencing the SCE baseline. Because the circumstances of the study and the procedure employed were standard we examined such confounding factors as sex and smoking habits. Neither in controls nor in workers did participate alcoholics, therefore it was not taken into consideration.

For chromosomal aberrations sex does not appear to be confounding factor, but for SCEs there might be differences [25]. In our controls no significant difference was found between males and females (Table 3). Such a comparison was not informative among occupationally exposed people due to the large inhomogeneity of exposure categories.

Smoking is one of the most widely examined confounding factors. We compared only two exposed groups to controls, because the number of persons was sufficiently comparable only in groups II and VII. The number of chromatid and chromosome type aberrations was also favourably low and comparable to the controls. Neither in aberration nor in SCE frequency we could demonstrate any difference between smokers and non smokers (Table 5).

There are a number of reports indicating a small but significant increase of SCEs in lymphocytes of persons inhaling cigarette smoke [26-28]; however, others [29] could not prove the phenomenon.

Table 5. - *Chromosomal aberrations and SCEs in controls and in occupationally exposed persons*

Number of smokers/ non smokers	Smokers no. of aberrations (%) and SCEs (*)					Non smokers no. of aberrations (%) and SCEs (*)				
	chromatide deletions	acentric fragments	dicentrics	total	SCE/cell ± S.D. (range of SCE)	chromatide deletions	acentric fragments	dicentrics	total	SCE/cell ± S.D. (range of SCE)
Controls 29/47	12 (0.41)	13 (0.45)	2 (0.07)	27 (0.93)	5.42 ± 0.64 (4.49-7.52)	12 (0.26)	8 (0.17)	1 (0.02)	21 (0.45)	5.56 ± 0.67 (4.488-7.64)
II Research labs using isotopes 1/16	8 (0.67)	5 (0.42)	2 (0.17)	15 (1.25)	7.90 ± 1.42 (5.20-10.11)	10 (0.63)	14 (0.88)	60 (0.38)	30 (1.88)	7.13 ± 1.20 (5.98-9.60)
VIII Vinyl-chloride exposure 12/25	16 (1.33)	4 (0.33)	—	21 (1.75)	7.45 ± 1.15 (5.41-10.52)	32 (1.28)	7 (0.25)	5 (0.18)	44 (1.57)	7.46 ± 1.59 (5.30-10.48)

(*) Data between smokers and non smokers did not differ significantly either for aberration, or for SCE values

Our negative results might be explained either with moderate smoking of smokers or with "passive smoking" of non smokers around smokers. We can also establish, that smoking did not influence the sensitivity to the exposure of occupational mutagens.

In order to validate any conclusion arrived from this study, we would like to quote Carrano and Natarajan [30]: "human specimen from exposed and control populations are a precious resource to the scientific community. Whenever possible, these specimens should be made available to interested collaborators for the concurrent or subsequent application of other genetic endpoints relevant to the suspected exposure". The importance of these examinations was twofold; we investigated consequently 211 controls and 163 exposed persons under the same laboratory conditions and with standard procedures. We compared chromosomal aberrations and sister chromatid exchanges in groups of people occupationally exposed to radiation and/or to chemicals, and these persons were representatives of our Hungarian occupational communities, where we will also be able to use these data for retrospective studies.

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