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"What are Sister Chromatid Exchanges?"

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DISCLAIMER

In the preceding paper, methods for detecting sister chromatid exchanges (SCEs) (Latt, 1973; Perry and Wolff, 1974), and some applications of the SCE test were described. While this test is being widely used in investigations of the properties of carcinogens and mutagens, the molecular mechanism and biological significance of the exchange events is still unknown. It is therefore important that we attempt to assess the relations of SCEs to chromosome aberration formation, DNA repair processes, and mutation.

i SCE and chromosome aberrations

Autoradiographic studies had shown that SCEs were induced by chromosome damaging agents such as UV (Rommelaere et al., 1973), X-rays (Gatti and Olivieri, 1973), or incorporated tritium (Gibson and Prescott, 1972), but it is now clear that high frequencies of chromosome aberrations are not necessarily associated with large numbers of SCEs. In investigations of SCE, aberrations and repair, it was of interest to examine not only experimentally induced chromosome damage, but also situations where there is a high level of spontaneous chromosome damage, as in the rare hereditary disorders ataxia telangiectasia (AT), Fanconi's anaemia (FA) and Bloom's syndrome (BS). Soon after the description of the new staining techniques for differentiation of sister chromatids, it was shown that although BS cells had very high spontaneous SCE frequencies (Chaganti et al., 1974), the SCE levels in cells from the other chromosome instability syndromes, AT and FA,were normal despite the large numbers of chromosome aberrations (Galloway and Evans, 1975; Chaganti et al., 1974; Sperling et al., 1975). It was also shown that while X-rays induced large numbers of chromosome aberrations in Chinese hamster ovary (CHO) cells, there was only a slight increase in SCE frequency (Perry and Evans, 1975). Conversely, after

treatment with chemical mutagens, extremely high levels of SCEs were produced in cells showing minimal amounts of chromosome damage (Latt, 1974; Kato, 1974a; Solomon and Bobrow, 1975; Perry and Evans, 1975).

A detailed examination of "harlequin-stained" chromosomes established that SCE is not an integral part of the process of aberration formation, since the exchanges occurred at the sites of only a proportion of X-ray-induced chromosome breaks (Wolff and Bodycote, 1975). Similarly, in cells from patients with Bloom's syndrome (BS), although there were very high frequencies of spontaneous SCEs and of aberrations (Chaganti et al., 1974), the locations of SCEs were not related to the distribution of break points involved in chromatid interchanges (Schroeder, 1975).

Further evidence for differing origins of X-ray-induced SCEs and aberrations came from observations on the timing of SCE induction with respect to the cell cycle. Cells treated with X-rays during G2 contain many chromatid aberrations at the subsequent metaphase (M1), whereas after exposure to UV light a period of DNA synthesis is necessary before the lesions are expressed as aberrations that are then visible at the second mitotis (M2); (Ikushima and Wolff, 1974). The induction of SCEs also requires a DNA replication period (Wolff et al., 1974) so that X-irradiation of cells in G2 did not affect SCE levels at M1 (Perry and Evans, 1975) despite the obvious chromatid damage.

A discrepancy between chromosome breaking ability and potency in induction of SCEs has been demonstrated for a range of chemicals in UV-sensitive xeroderma pigmentosum (XP) cells (Wolff et al., 1977). Like UV light, the mutagen 4-NQO (4-nitroquinoline-1-oxide) induced abnormally high levels of chromosome damage in XP cells, and both UV and 4-NQO caused exaggerated increases in SCE levels in XP cells compared with

normal cells. However this disproportionately large increase in SCE levels was also seen after exposure to chemicals such as MNNG (N-methyl-N-nitro-nitrosoguanidine), a monofunctional alkylating agent that produces only normal amounts of chromosome damage in XP cells.

ii SCE and DNA Repair

The above observations suggest that the lesions that ultimately result in SCE formation are induced more efficiently by UV and some chemicals than by X-rays. It is likely that SCEs arise as a consequence of lesions such as crosslinks that cause deformations or "kinks" in the DNA backbone, and this would explain the inefficiency of ionising radiations in stimulation of SCE, since the predominant lesions induced by X-rays are single- and double-stranded DNA breaks that are usually rejoined very rapidly.

The agents that induce SCE also provoke DNA repair, and it was suggested that SCE might reflect some cellular repair mechanism (Kato, 1973; Bender et al., 1974; Wolff et al., 1974). An association with post-replication repair (PRR) seemed possible because PRR in bacteria involves recombination, and because UV-induced SCE levels were said to be depressed by caffeine (Kato, 1973), thought to be an inhibitor of PRR in some cell types. An association between repair capacity and meiotic recombination had also been suggested because of observations on chiasma frequency and radiation sensitivity in barley (Riley and Miller, 1966) and in a human male (Pearson et al., 1970).

Studies on harlequin chromosomes described by Wolff and Perry (1975) demonstrated that SCE does not result from single DNA strand exchange as postulated by Bender et al. (1973), and the results were consistent with the concept that SCEs are double-stranded exchange events.

Unfortunately the mechanism of PRR in mammalian cells is unknown, and the involvement of recombination has been questioned. During bacterial recombination repair, gaps that are left in the newly synthesised DNA strand opposite lesions such as dimers, are filled in by recombination with the complementary DNA strand (Rupp et al., 1971). However there is some evidence that in mammalian cells these gaps are filled in by de novo DNA synthesis (Lehmann, 1972), rather than by strand exchange. An alternative model invokes the process of strand displacement and branch migration, where an intact DNA strand from the sister chromatid is "borrowed" to function as a template and thus bypass the lesion (Higgins et al., 1976).

The evidence that recombination occurs in mammalian somatic cells includes the apparent transfer of damage induced by UV in the DNA, to "daughter" strands synthesised after irradiation. The presence of dimers in the newly synthesised DNA was inferred from the existence of sites susceptible to a'phage endonuclease known to "nick" DNA at sites adjacent to dimers (Buhl and Regan, 1973; Meneghini and Hanawalt, 1976). Secondly, the recombination models described by Whitehouse (1963) and by Holliday (1964) require an intermediate "hybrid" or heteroduplex DNA molecule, and there is some evidence that such a molecule exists and that the amount of hybrid DNA is increased after treatment with UV (Rommelaere and Miller-Faures, 1975) or with Mitomycin C (Moore and Holliday, 1976).

Studies on the X chromosome of Chinese hamster cells indicated that the sites of SCEs, induced in BrdU-substituted chromosomes by fluorescent light, corresponded to the regions undergoing DNA synthesis at the time of illumination (Kato, 1974b). Since it is also clear that a period of DNA synthesis is necessary for a lesion to manifest itself as a SCE, some initiating event at the replication fork seemed likely (Perry and Evans,

1975). Any process that increased the susceptibility of DNA that is partially denatured during replication might thus increase the numbers of SCEs generated. The depressed rate of DNA chain elongation detected in cells from patients with Bloom's syndrome (Hand and German, 1975; Gianelli et al., 1977) may thus contribute to the high spontaneous rate of SCEs in these cells, as the vulnerable uncoiled DNA may be exposed for longer periods than is normal, providing increased opportunities for exchange. It is interesting, however, that while the rate of DNA chain elongation may decrease during "senescence" of cells in vitro (Petes et al., 1974), there is only one report of raised SCE levels in "old" tissue culture cells (Kato and Stich, 1976). In studies of in vitro ageing, the exact "passage level" of the cells tested is important, as this has been shown to affect markedly the results of tests for repair capacity (Painter et al., 1973).

One approach to investigating the possible association of SCE and repair is to examine repair-deficient cells such as excision-defective XP cells. Repair defects are also implicated in AT and in FA (table 1) yet in these diseases and in XP, "background" SCE levels are normal (see table). It is noteworthy that in BS cells, where SCE levels are extremely high, there is as yet no evidence for a specific repair defect, but normal semiconservative DNA synthesis is itself disturbed (Hand and German, 1975; Gianelli et al., 1977). Studies of induced SCE frequencies in repair-deficient cells may yield more information than "background" levels (table 1). Lymphocytes from patients with FA are apparently inefficient in removal of crosslinks induced by Mitomycin C (MMC) (Sasaki and Tonomura, 1973) and are also unable to produce normal high levels of SCEs in response to MMC (Latt et al., 1975) (table 1). In contrast, cells from AT patients

show a normal SCE response to MMC, ethyl methane sulphonate (EMS) and the cytotoxic drug Adriamycin (AM); [Galloway, in press].

The conflicting evidence on SCE, aberration induction, and repair led to the idea that there is more than one major pathway involved in SCE production, and some recent experiments on Chinese hamster D-6 cells were designed to test this hypothesis. Kato (1977) made use of the ability of fluorescent light to induce strand breaks specifically in DNA substituted with BrdU. By manipulating cell cultures, it was possible to illuminate during S-phase, chromosomes that had incorporated BrdU into either one or three out of the four DNA polynucleotide strands. The prereplication DNA was unifilarly substituted with BrdU in both cases. If SCE occurred only when the replication fork reached a strand break, the frequency of light-induced SCEs would be the same in both types of chromosomes since there should be similar numbers of replication forks. However, if SCE also resulted from strand breakage in replicated DNA, the more heavily substituted chromosomes, having more strand breaks, should show more SCEs. The results of fluorescent light illumination during the S phase (6 h before harvest) showed very little difference in SCE frequency between the two types of chromosomes, although the trifilarly substituted chromosomes had a slight excess of SCEs. This was interpreted as showing that strand breaks at the replication forks were the predominant cause of SCEs under these conditions, but that there was also a small contribution by breaks in post-replication DNA. The latter suggestion was apparently confirmed by the levels of light-induced SCEs after treatment with caffeine, a compound which inhibits repair in certain systems. Following a post-treatment with caffeine, the more highly-substituted chromosomes showed many more SCEs than the lightly substituted ones, suggesting that if repair of the light-induced

damage were prevented by caffeine, the lesions remaining in the replicated DNA were able to induce SCEs. In view of the fact that SCE cannot be induced by exposure during G2 to mutagens or fluorescent light, it seems that the lesions can provoke SCE in newly-replicated DNA only while cells are still in S phase, and not in G2 chromatin. The implications of Kato's results are that caffeine may inhibit excision of fluorescent-light induced damage, but does not prevent some post-replication repair mechanism that is responsible for SCE production. The results suggested that the amount of unexcised damage remaining in the DNA was reflected in the SCE frequency, in accordance with the conclusions of Wolff et al. (1977) from their experiments with chemical mutagen treatment of excision-defective XP cells.

iii SCE and Mutagenesis

There is much discussion at present about possible assays for mutagens and carcinogens, with the important aim of finding reliable tests to screen potentially dangerous compounds. SCE frequencies are a very sensitive test of exposure to some mutagens and the scope of the test in vitro can be widened to detect compounds that require metabolic activation (Stetka and Wolff, 1976b; Natarajan et al., 1976) by the inclusion of a preparation of liver microsomes (Ames et al., 1973). The levels of SCEs may also be assessed following in vivo exposure to chemical compounds by culturing blood lymphocytes in the presence of BrdU (Perry and Evans, 1975; Stetka and Wolff, 1976a). It is also possible to treat the test animals with BrdU and obtain sister chromatid differentiation in direct preparations of cells from bone marrow (Vogel and Bauknecht, 1976) and testis (Allen and Latt, 1976).

Work is in progress to compare results of several tests for mutagenicity and carcinogenicity, using a wide range of chemicals, and it is already known that "the ability of an alkylating agent to induce SCEs seems to bear no simple direct relationship to its efficiency in inducing point mutations in bacteria"(Perry and Evans, 1975). Also some compounds, such as acetylaminofluorene (AAF) did not increase SCEs in CHO cells even in conjunction with a metabolic activating system (Takehisa and Wolff, in press) although a similar mixture was known to be mutagenic in the Salmonella test of Ames (Ames et al., 1973). It is therefore crucial that we ascertain whether SCE truly reflects mutagenic events in mammalian cells.

Some SCEs occur at the sites of gross chromosomal aberrations and must be associated with mutation in these cases at least. If recombination is involved in the generation of SCEs, there is the possibility of errors just as mutations are associated with recombination in bacteria (Witkin, 1969) and in meiotic yeast cells (Magni, 1963).

In some interesting new work on Chinese hamster cells, the frequencies of mutation to azaguanine resistance at various doses of chemical mutagens were compared with SCE levels (A.V. Carrano, personal communication). The chemicals tested showed differing potencies as mutagens that fell into the same relative order as their efficiencies in induction of SCEs. However, certain compounds were much more effective in one test than in the other, probably due to the variety of DNA lesions produced. Clearly certain types of damage are more likely to provoke SCE than others.

It will be necessary to test thoroughly the correlation of SCE with various specific types of mutation, autosomal or sex chromosome-linked, frameshift, deletion, or point mutations, before we can draw conclusions on the molecular events implicated, but clearly the processes involved in SCE formation are complex.

In conclusion, we may say that SCEs are not simply related to chromosome aberrations or to any one known repair mechanism. They may involve a recombination event, often instituted at the replication fork, but also provoked by any unrepaired damage in the replicated DNA. The molecular mechanism of SCE is unknown and the investigation of the relationship of SCE to mutation is only beginning to yield information.

Table 1 The "Chromosome Instability Syndromes" and Xeroderma Pigmentosum.

	Ataxia Telangiectasia	Fanconi's Anaemia	Bloom's Syndrome	Xeroderma Pigmentosum
Spontaneous Chromosome Aberrations	+[1]	+[2]	+[3]	-[4]
High "Background" SCE	-[5,8]	-[7]	+[8]	-[9]
Increased Sensitivity To:*		+[27]		
X- and γ-Rays	+[10,11]	-[26,29]	+[11]	-[12,13]
Anoxic γ-Rays	+[22]			
UV	-[17,22]	+[15,19]	+[24]	+[4,13]
Chemical Mutagens	+[18]	+[19]		+[20,21]
(Monofunctional Alkylating Agents)	+[18]	-[19,29]		-[5]
Repair Defect**				
Strand-Break Rejoining	-[14]			
Cross-Link Removal		+[19]		
Excision:				
UV Damage	-[22]	+‡[15]	-[17]	(-[a])[32] +[13]
γ Damage		+‡ψ[28]		
Anoxic γ Damage	+[22]			+[16]
Post-Replication Repair			-[24]	(+[a])[30] -[31]
Photoreactivation				+ [25]

Footnotes for Table 1

* Chromosome aberrations or cell survival.

** + = defect identified.

\- = apparently normal.

‡ at high doses of UV.

‡‡ in two out of four patients.

a "Variant" XP with normal excision repair.

Some of the data in this table are conflicting, possibly due partly to differences among laboratories in methods and criteria used, but also partly to possible genetic heterogeneity in these diseases.

Table 1: Bibliography

1. Hecht et al., 1966
2. Schroeder et al., 1964
3. German, 1964
4. Parrington et al., 1971
5. Cleaver, 1971
6. Galloway and Evans, 1975
7. Sperling et al., 1975
8. Chaganti et al., 1974
9. Wolff et al., 1975
10. Rary et al., 1974
11. Higurashi and Conen, 1973
12. Kleijer et al., 1970
13. Cleaver, 1968
14. Taylor et al., 1975
15. Poon et al., 1974
16. Setlow et al., 1976
17. Cleaver, 1970
18. Hoar and Sargent, 1976
19. Sasaki and Tonomura, 1973
20. Stich and San, 1971
21. Stich et al., 1973
22. Paterson et al., 1976
23. Lehmann et al., 1975
24. Gianelli et al., 1977
25. Sutherland et al., 1975
26. K. Buckton, unpublished data
27. Higurashi and Conen, 1971
28. Remsen and Cerutti, 1976
29. Finkelberg et al., 1974
30. Fornace et al., 1976
31. Buhl et al., 1972
32. Burk et al., 1971

References

Allen, J.W., and Latt, S.A. (1976). Analysis of sister chromatid exchange formation in vivo in mouse spermatogonia as a new test system for environmental mutagens. Nature 260, 449-451.

Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D. (1973). Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection. Proc. Natl. Acad. Sci. (US) 70, 2281-2285.

Bender, M. A, Griggs, H.G., and Walker, P.L. (1973). Mechanisms of chromosomal aberration production. I. Aberration induction by ultraviolet light. Mutation Res. 20, 387-402.

Bender, M. A, Griggs, H.G., and Bedford, J.S. (1974). Recombinational DNA repair and sister chromatid exchanges. Mutation Res. 24, 117-123.

Buhl, S.N., and Regan, J.D. (1973). Repair endonuclease-sensitive sites in daughter DNA of ultraviolet-irradiated human cells. Nature 246, 484.

Buhl, S.N., Stillman, R.M., Setlow, R.B., and Regan, J.D. (1972). DNA chain elongation and joining in normal human and xeroderma pigmentosum cells after ultraviolet irradiation. Biophys. J. 12, 1183-1191.

Burk, P.G., Yuspa, J.H., Lutzner, M.A., and Robbins, J.H. (1971). Xeroderma pigmentosum and DNA repair. Lancet i 601.

Chaganti, R.S.K., Schonberg, S., and German, J. (1974). A manyfold increase in sister chromatid exchanges in Bloom's syndrome lymphocytes. Proc. Natl. Acad. Sci. (US) 71, 4508-4512.

Cleaver, J.E. (1968). Defective repair replication of DNA in xeroderma pigmentosum. Nature 218, 652-656.

Cleaver, J.E. (1970). DNA damage and repair in a light-sensitive human skin disease. J. Invest. Dermatol. 54, 181-195.

Cleaver, J.E. (1971). Repair of alkylation damage in ultraviolet-sensitive (Xeroderma Pigmentosum) human cells. Mutation Res. 12, 453-462.

Finkelberg, R., Thompson, M., and Siminovitch, L. (1974). Survival after treatment with EMS, gamma rays, and Mitomycin C of skin fibroblasts from patients with Fanconi's anaemia. Amer. J. Hum. Genet. 26, A30.

Fornace, A.J., Kohn, K.W., and Kann, H.E. (1976). DNA single-strand breaks during repair of UV damage in human fibroblasts and abnormalities of repair in xeroderma pigmentosum. Proc. Natl. Acad. Sci. (US) 73, 39-43.

Galloway, S.M., and Evans, H.J. (1975). Sister chromatid exchanges in human chromosomes from normal individuals and patients with ataxia telangiectasia. Cytogenet. Cell Genet. 15 17-29.

Gatti, M., and Olivieri, G. (1973). The effect of X-rays on labelling patterns of M1 and M2 chromosomes in Chinese hamster cells. Mutation Res. 17, 101-112.

German, J. (1964). Cytological evidence for crossing-over in vitro in human lymphoid cells. Science 144, 298-301.

Gianelli, F., Benson, P.F., Pawsey, S.A., and Polani, P.E. (1977). Ultraviolet light sensitivity and delayed DNA chain maturation in Bloom's syndrome fibroblasts. Nature 265, 466-469.

Gibson, D.A., and Prescott, D.M. (1972). Induction of sister chromatid exchanges in rat kangaroo chromosomes. Exp. Cell Res. 86, 209-214.

Hand, R., and German, J. (1975). A retarded rate of DNA chain growth in Bloom's syndrome. Proc. Natl. Acad. Sci. (US) 72, 758-762.

Hecht, F., Koler, R.D., Rigas, D.A., Dahnke, G.S., Case, M.P., Tisdale, V., and Miller, R.W. (1966). Leukaemia and lymphocytes in ataxia telangiectasia. Lancet ii 1193.

Higgins, N.P., Kato, K., and Strauss, B. (1976). A model for replication repair in mammalian cells. J. Mol. Biol. 101, 417-425.

Higurashi, M., and Conen, P.E. (1971). In vitro chromosomal radiosensitivity in Fanconi's anaemia. Blood 38, 336-342.

Higurashi, M., and Conen, P.E. (1973). In vitro chromosomal radiosensitivity in chromosomal breakage syndromes. Cancer 32, 380-383.

Hoar, D.I., and Sargent, P. (1976). Chemical mutagen hypersensitivity in ataxia telangiectasia. Nature 261, 590-592.

Holliday, R. (1964). A mechanism for gene conversion in fungi. Genet. Res. 5, 282-304.

Ikushima, T., and Wolff, S. (1974). UV-induced chromatid aberrations in cultured Chinese hamster cells after one, two, or three rounds of DNA replication. Mutation Res. 22, 193-201.

Kato, H. (1973). Induction of sister chromatid exchanges by UV light and its inhibition by caffeine. Exp. Cell Res. 83, 383-390.

Kato, H. (1974a). Induction of sister chromatid exchanges by chemical mutagens and its possible relevance to DNA repair. Exp. Cell Res. 85, 239-247.

Kato, H. (1974b). Possible role of DNA synthesis in formation of sister chromatid exchanges. Nature 252, 739-741.

Kato, H. (1977). Mechanisms for sister chromatid exchanges and their relation to the production of chromosomal aberrations. Chromosoma (Berl.) 59, 179-191.

Kato, H., and Stich, H.F. (1976). Sister chromatid exchanges in ageing and repair-deficient human fibroblasts. Nature 260, 447-448.

Kleijer, W.J., Lohman, P.H.M., Mulder, M.P., and Bootsma, D. (1970). Repair of X-ray damage in DNA of cultivated cells from patients having xeroderma pigmentosum. Mutation Res. 9, 517-523.

Latt, S.A. (1973). Microfluorimetric detection of deoxyribonucleic acid replication in human metaphase chromosomes. Proc. Natl. Acad. Sci. (US) 70, 3395-3399.

Latt, S.A. (1974). Sister chromatid exchanges, indices of human chromosome damage and repair: detection by fluorescence and induction by Mitomycin C. Proc. Natl. Acad. Sci. (US) 71, 3162-3166.

Latt, S.A., Stetten, G., Juergens, L.A., Buchanan, G.R., and Gerald, P.S. (1975). Induction by alkylating agents of sister chromatid exchanges and chromatid breaks in Fanconi's anaemia. Proc. Natl. Acad. Sci. (US) 72, 4066-4070.

Lehmann, A.H.R. (1972). Postreplication repair of DNA in ultraviolet irradiated mammalian cells. J. Mol. Biol. 66, 319-337.

Lehmann, A.R., Kirk-Bell, S., Arlett, C.F., Paterson, M.C., Lohman, P.H.M., deWeerd-Kastelein, E.A., and Bootsma, D. (1975). Xeroderma pigmentosum cells with normal levels of excision repair have a defect in DNA synthesis after UV irradiation. Proc. Natl. Acad. Sci. (US) 72, 219-223.

Magni, G.E. (1963). The origin of spontaneous mutation during meiosis. Proc. Natl. Acad. Sci. (US) 50, 975-980.

Meneghini, R., and Hanawalt, P. (1976). T4-endonuclease V-sensitive sites in DNA from ultraviolet irradiated human cells. Biochim. Biophys. Acta 425, 428-437.

Moore, P.D., and Holliday, R. (1976). Evidence for the formation of hybrid DNA during mitotic recombination in Chinese hamster cells. Cell 8, 573-579.

Natarajan, A.T., Tates, A.D., Van Buul, P.P.W., Meijers, M., and de Vogel, N. (1976). Cytogenetic effects of mutagens/carcinogens after activation in a microsomal system in vitro. I. Induction of chromosome aberrations and sister chromatid exchanges by diethylnitrosamine (DEN) and dimethylnitrosamine (DMN) in CHO cells in the presence of rat liver microsomes. Mutation Res. 37, 83-90.

Painter, R.B., Clarkson, J.M., and Young, B.R. (1973). Ultraviolet-induced repair replication in aging diploid human cells (WI-38). Radiation Res. 56, 560-564.

Parrington, J.M., Delhanty, J.D.A., and Baden, H.P. (1971). Unscheduled DNA synthesis, UV-induced chromosome aberrations and SV40 transformation in cultured cells from xeroderma pigmentosum. Ann. Hum. Genet. 35, 149-160.

Paterson, M.C., Smith, B.P., Lohman, P.H.M., Anderson, A.K., and Fishman, L. (1976). Defective excision repair of gamma-ray damaged DNA in human (ataxia telangiectasia) fibroblasts. Nature 260, 444-447.

Pearson, P.L., Ellis, J.D., and Evans, H.J. (1970). A gross reduction in chiasma formation during mitotic prophase and a defective DNA repair mechanism associated with a case of human male infertility. Cytogenetics 9, 460-467.

Perry, P., and Wolff, S. (1974). New Giemsa method for the differential staining of sister chromatids. Nature 251, 156-158.

Perry, P., and Evans, H.J. (1975). Cytological detection of mutagen-carcinogen exposure by sister chromatid exchange. Nature 258, 121-125.

Petes, T.D., Farber, R.A., Tarrant, G.M., and Holliday, R. (1974). Altered rate of DNA replication in ageing human fibroblast cultures. Nature 251, 434-436.

Poon, P.K., O'Brien, R.L., and Parker, J.W. (1974). Defective DNA repair in Fanconi's anaemia. Nature 250, 223.

Rary, J.M., Bender, M. A, and Kelly, T.E. (1974). Cytogenetic studies of ataxia telangiectasia. Am. J. Hum. Genet. 26, 70A.

Remsen, J.F., and Cerutti, P.A. (1976). Deficiency of gamma-ray excision repair in skin fibroblasts from patients with Fanconi's anaemia. Proc. Natl. Acad. Sci. (US) 73, 2419-2423.

Riley, R., and Miller, T.E. (1966). The differential sensitivity of desynaptic and normal genotypes of barley to X-rays. Mutation Res. 3, 355-359.

Rommelaere, J., and Miller-Faurès, A. (1975). Detection by density equilibrium centrifugation of recombinant-like DNA molecules in somatic mammalian cells. J. Mol. Biol. 98, 195-218.

Rommelaere, J., Susskind, M., and Errera, M. (1973). Chromosome and chromatid exchanges in Chinese hamster cells. Chromosoma 41, 243-257.

Rupp, W.D., Wilde, C.E., Reno, D.L., and Howard-Flanders, P. (1971). Exchanges between DNA strands in ultraviolet-irradiated Escherichi coli. J. Mol. Biol. 61, 25-44.

Sasaki, M.A., and Tonomura, A. (1973). A high susceptibility of Fanconi's anaemia to chromosome breakage by DNA crosslinking agents. Cancer Res. 33, 1829-1836.

Schroeder, T.M. (1975). Sister chromatid exchanges and chromatid interchanges in Bloom's syndrome. Humangenetik 30, 317-323.

Schroeder, T.M., Auschwitz, F., and Knopp, A. (1964). Spontane Chromosomen - aberrationen bei familarer Panmyelopathie. Humangenetik 1, 194-196.

Setlow, R.B., Faulcon, F.M., and Regan, J.D. (1976). Defective repair of gamma-ray-induced DNA damage in xeroderma pigmentosum cells. Int. J. Radiat. Biol. 29, 125-136.

Solomon, E., and Bobrow, M. (1975). Sister chromatid exchanges - a sensitive assay of agents damaging human chromosomes. Mutation Res. 30, 273-278.

Sperling, K., Wegner, R-D., Riehm, H., and Obe, G. (1975). Frequency and distribution of sister chromatid exchanges in a case of Fanconi's anaemia. Humangenetik 27, 227-230.

Stetka, D.G., and Wolff, S. (1976). a. Sister chromatid exchange as an assay for genetic damage induced by mutagen - carcinogens. I. In vivo test for compounds requiring metabolic activation. Mutation Res. 41, 333-342.

b. II. In vitro test for compounds requiring metabolic activation. Mutation Res. 41, 343-350.

Stich, H.F., and San, R.H.C. (1971). Reduced DNA repair synthesis in xeroderma pigmentosum cells exposed to the oncogenic 4-nitroquinoline-1-oxide and 4-hydroxylamine-1-oxide. Mutation Res. 13, 279-282.

Stich, H.F., San, R.H.C., and Kawazoe, Y. (1973). Increased sensitivity of xeroderma pigmentosum cells to some chemical carcinogens and mutagens. Mutation Res. 17, 127-137.

Sutherland, B.M., Rice, M., and Wagner, E.K. (1975). Xeroderma pigmentosum cells contain low levels of photoreactivating enzyme. Proc. Natl. Acad. Sci. (US) 72, 103-107.

Taylor, A.M.R., Harnden, D.G., Arlett, C.F., Harcourt, S.A., Lehmann, A.R., Stevens, S., and Bridges, B.A. (1975). Ataxia telangiectasia: a human mutation with abnormal radiation sensitivity. Nature 258, 427-429.

Vogel, W., and Bauknecht, T. (1976). Differential chromatid staining by in vivo treatment as a mutagenicity test system. Nature 260, 448-449.

Whitehouse, H.L.K. (1963). A theory of crossing-over by means of hybrid deoxyribonucleic acid. Nature 199, 1034-1040.

Witkin, E.M. (1969). Ultraviolet-induced mutation and DNA repair. Ann. Rev. Microbiol. 23, 487-514.

Wolff, S., and Bodycote, J. (1975). The induction of chromatid deletions in accord with the breakage and reunion hypothesis. Mutation Res. 29, 85-91.

Wolff, S., and Perry, P. (1975). Insights on chromosome structure from sister chromatid exchange ratios and the lack of both isolabelling and heterolabelling as determined by the FPG technique. Exp. Cell Res. 93, 23-30.

Wolff, S., Bodycote, J., and Painter, R.B. (1974). Sister chromatid exchanges induced in Chinese hamster cells by UV irradiation of different stages of the cell cycle: the necessity for cells to pass through S. Mutation Res. 25, 73-81.

Wolff, S., Bodycote, J., Thomas, G., and Cleaver, J.E. (1975). Sister chromatid exchange in xeroderma pigmentosum cells that are defective in DNA excision repair or post-replication repair. Genetics 81, 349-355.

Wolff, S., Rodin, B., and Cleaver, J.E. (1977). Sister chromatid exchanges induced by mutagenic carcinogens in normal and xeroderma pigmentosum cells. Nature 265, 347-349.