Testing for mutagenicity

from E. H. R. Ford

A RELIABLE method of assessing the mutagenicity of chemical and physical agents in mammalian cells would be invaluable. Visible chromosome damage such as breaks, and translocations has been used, but has proved rather disappointing so far; it is not as sensitive as could be wished, and while it can be effective for heavy doses of some mutagens, such as X rays, it often yields unsatisfactory results in terms of normal dose rates of ingested substances (as seen for instance in the confused literature on chromosomal breakage and LSD). Perry and Evans (*Nature* **258**, 121; 1975) showed that the number of sister chromatid exchanges (SCEs) per cell is a far more sensitive indicator of exposure to both physical and chemical mutagens than is the number of visible chromosomal aberrations, but it has not yet been proven that the presence of increased numbers of SCEs necessarily indicates actual damage to the genetic information of the cell. But now Carrano *et al.* (page 551 of this issue) have provided stronger evidence that the number of SCEs seen in cells after treatment with a range of known mutagens may be directly related to genetic damage and mutation rate, in which case it could represent a sensitive and easily quantified test of mutagenicity.

Sister chromatid exchange can be seen in chromosomes studied at the metaphase stage of cell division. At this stage each chromosome is made up of two equal chromatids which arise when the chromosomal DNA is replicated at the synthetic (S) phase of the cell cycle, a few hours before cell division starts. If material has been exchanged between these two sister chromatids by the metaphase stage it means that DNA breakage and repair must have taken place between S phase and metaphase. Precise interchange of material need not of itself alter the genetic information of a cell, so the significance of visible SCE as a measure of possible genetic damage or mutation has not so far been clear.

Although SCE was described by J. H. Taylor *et al.* 20 years ago (*Proc. natn Acad. Sci. U.S.A.* **43**, 122; 1957), using an autoradiographic technique, it is only since S. A. Latt (*Proc. natn Acad. Sci. U.S.A.* **70**, 3395; 1973) introduced an optical method for differentiating sister chromatids that SCE has readily been studied. A newly replicated chromatid which has incorporated the thymidine analogue BUdR can be differentiated from its older sister by fluorescent, Giemsa staining or immunological techniques (since the BUdR quenches the fluorescent or staining property of the chromatin).

The baseline SCE frequency in untreated human lymphocytes is 5–15 per cell (Latt & Juergens in *Population Cytogenetics* (Eds Hook, E. B. & Porter, I. H., Academic Press, 237; 1977). Alkylating agents such as ethylmethanesulphonate, mitomycin C or nitrogen mustard (which can all also induce visible chromosomal damage) considerably increase the number of SCEs per cell at concentrations where no other visible morphological damage is caused to chromosomes, indicating that SCE number is a sensitive test for chromosome damage.

Carrano *et al.* have now shown that in Chinese hamster ovary cells there is a strong and linear relationship between the induction of SCEs and of mutations producing resistance to 8-azaguanine (mutations mainly at a particular locus, the hypoxanthine phosphoribosyl transferase (HPRT) locus.) They used four mutagenic agents; the alkylating agents, ethylmethanesulphonate (EMS) and N-ethyl-N-nitrosourea (ENU), mitomycin C (MMC) which is also a cross-linking agent, and proflavine sulphate (PRO), which intercalates into DNA. Each agent produced increases in the SCE and mutation rates, and for each there was a linear relationship between SCE and mutation rate—but this was different for each agent. ENU was the least efficient inducer of SCEs compared with mutations, and MMC the most efficient. The authors have been able to calculate the number of mutations per cell which correspond to one SCE, ranging from 0.08 for MMC to 1.2 for ENU.

If certain extrapolations can be made, namely that the marker used gives a representative mutation rate comparable to that at other loci, that human cells behave similarly to those of the Chinese hamster and that the SCE/mutation ratio *in vitro* can be extrapolated to cells *in vivo*, it would be possible to estimate the mutagenicity of various physical and chemical agents simply by counting the number of SCEs found in human lymphocytes.

Carrano *et al.*'s findings need to be confirmed and the validity of these extrapolations determined. But if Carrano *et al.*'s suggestions are confirmed we may soon have a greatly improved, simple and direct method of assessing the mutagenicity of all sorts of agents.

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Preplanetary disk?

from Andrew Fabian

THE formation of stars is shrouded by dust. The massive gas clouds within which they form by gravitational collapse are cold and seeded with dust grains. Optical radiation from the newborn star is scattered and absorbed by these dust clouds, then reradiated at infrared wavelengths. Consequently it is often easier to deduce more about the properties of the gas and dust than the star. This means that little is known observationally about this important phase of a star's life.

From a theoretical point of view the situation is somewhat happier, at least until the observations improve. The collapse and fragmentation of a cold gas cloud under gravity has been discussed for decades. Problems emerge, not the least of which are to do with the rotation and magnetisation of the star. Perfectly spherically symmetrical collapse seems most unlikely, especially when it is recalled that stars are observed to rotate at speeds up to and approaching breakup speed. Many stars are, moreover, members of binary (or multiple) pairs in orbit about each other. A collapsing rotating gas cloud is likely to flatten out and form a disk with a bulge in the centre—not too dissimilar in shape to our Galaxy. The bulge will form the stars and the disk what? Planets perhaps?—A tempting possibility considering the disk-like concentration of the major and many of the minor bodies of the Solar System. Gravitational collapse is halted within the central star, at least for the time being, by the onset of nuclear fusion, but accretion will continue within the disk until it is dispersed. Turbulent or magnetic viscosity in a disk as dense as might be associated with a newly forming star causes matter to spiral in at the expense of angular momentum, which flows outward. We have our friend the accretion disk, which has been much discussed in the context of accretion onto black holes, both in X-ray binaries and galactic nuclei. A start was made on modelling accretion disks around newly formed stars a few years ago by D. Lynden-Bell and J. Pringle (*Mon. Not. Roy. Astr. Soc.* **168**, 603; 1974). Clearly, observational evidence of such a disk around a newly formed star is of great interest.

R. I. Thompson, P. A. Strittmatter, E. F. Erickson, F. C. Witteborn and D. W. Strecker have made a good start (*Astrophys. J.* **218**, 170; 1977) by combining their own infrared spectra of some highly reddened emission-line objects with unpublished optical continuum data of one of the objects taken by S. Grandi. MWC 349 and LK Hα 107 are objects from the Mount Wilson, and Lick, catalogues of emis-

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