Biological dosimetry in astronauts

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Chromosome damage in peripheral blood cells is a sensitive indicator of radiation exposure that can provide an *in vivo* method for assessing radiation dose. Increased levels of cytogenetic damage in astronaut's blood lymphocytes after a mission provide a direct measurement of the effects of space radiation exposure and this datum can be used to measure radiation doses incurred during the flight. Although space radiation exposures can also be assessed using passive thermoluminescent dosimeters (TLDs) and plastic nuclear track detectors (PNTDs), multiple devices are required to detect all radiation types encountered in space, and all currently available devices have poor sensitivity to neutrons. In addition physical measurements only provide absorbed skin doses, which must be combined with computerized anatomical models and radiation transport codes to estimate the dose at different regions of the body. In contrast biodosimetry is internal and includes the effects of shielding provided by the body itself plus chromosome damage and shows excellent sensitivity to all types of radiation including neutrons. Biodosimetry provides information on individual sensitivity to radiation in the presence of confounding factors such as microgravity and other stress conditions. Moreover, chromosome damage may reflect cancer risk (Bonassi et al 2005), and biodosimetry values can therefore be used to validate and develop risk assessment models that can be used to characterize excess health risk incurred by crew members.

Cytogenetic biodosimetry methods have been used extensively for assessing terrestrial radiation exposures and remain the most sensitive *in vivo* indicator of dose available to date. The main cellular radiation target is the DNA, and radiation-induced damage in the DNA molecule can be visualized as aberrations in the chromosomes (breaks in the chromosomes or exchanges of DNA material between different chromosomes). Normal chromosomes contain a single condensed and constricted area called a centromere that helps the chromosome number to remain stable when a cell divides.

Figure 1. Examples of solid stained chromosomes, showing a dicentric chromosome (a chromosome with 2 centromeres) that results from the fusion of two broken chromosomes, a fragment from chromosome breakage, and a ring that results from fusion of the broken ends of a single chromosome.

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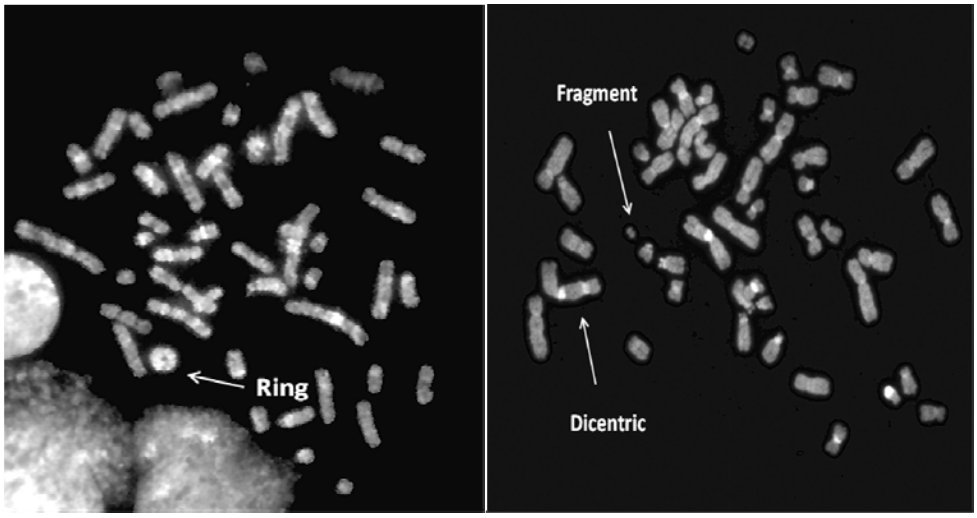

The first studies on the peripheral blood lymphocytes of crew members in the Gemini (Bender et al, 1967 and 1968) and Mir programs (Federenko et al, 2003, Testard et al, 1997) used solid Giemsa staining techniques to assess chromosome damage in the form of dicentrics, rings, and fragments. Results indicated that crew members who participated in flights lasting 3 weeks or less showed no significant elevation of chromosome damage post flight, whereas most crew members who participated in missions lasting 4-6 months had elevated chromosome damage post flight. Pooled data for individuals who had increased chromosome damage showed a post-flight dicentric yield that was roughly 3 times preflight values. However, large inter-individual variations were reported, with some individuals having no appreciable increase in dicentric yield post flight.

Evidence from these early cytogenetic studies strongly indicated that the radiation dose accumulated during a long-duration flight can induce measurable increases in the yield of chromosome damage, whereas the doses encountered during shorter missions of a few weeks or less are below the threshold for detection using this technique. However, the type of chromosomal aberration evaluated is an important factor when considering these data. All of the early astronaut studies focused on the detection of dicentric chromosomes. This technique has been used for many years to evaluate accidental radiation exposures because pre-exposure background levels are very low. It has been well documented that radiation-induced dicentrics undergo time-dependent decay in blood lymphocytes because they impede proper cell division. Dicentrics have been estimated to have an average half-life of about 3 years in human peripheral blood lymphocytes, but recent studies indicate that great inter-individual variability exists in decay rates. It would follow that the use of dicentric aberrations for biodosimetry analysis after missions lasting several months may not be reliable due to the loss of aberrant cells during the mission, and this may explain the inter-individual variations reported for post-flight yields of dicentrics. In addition, any significant inter-individual variability in the rate of loss of cells with dicentrics would indicate that yields could not be accurately corrected for elimination of this type of exchange from the blood.

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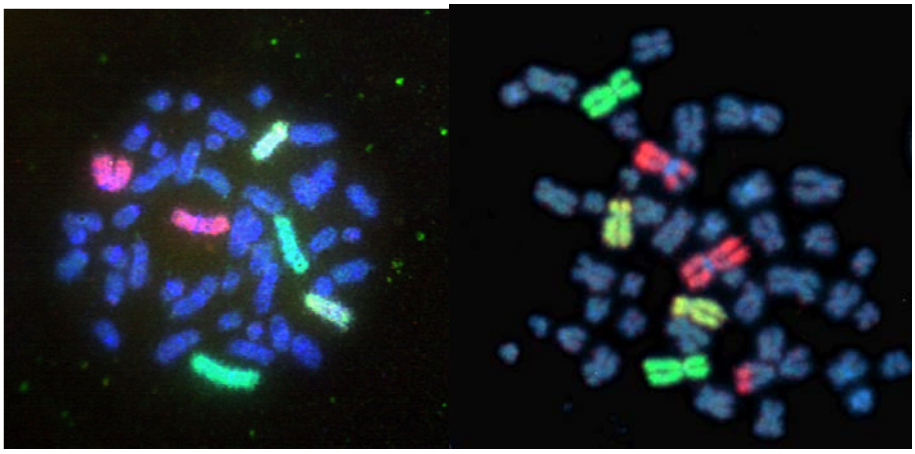
The introduction of the fluorescence *in situ* hybridization (FISH) chromosome painting technique radically improved the ease and accuracy of assessing yields of monocentric aberrations such as translocations (exchanges of material between two chromosomes that each retain a single centromere). With the FISH chromosome painting method, it is possible to "paint" individual chromosomes with different colors, and aberrations can be easily identified as multi-color chromosomes.

Figure 2. Example of FISH chromosome painting. The image on the left shows a cell with two normal copies of chromosome 1 (red), chromosome 2 (green), and chromosome 4 (yellow); the rest of the chromosomes are stained blue. The image on the right shows a cell with a translocation involving one copy of chromosome 1 and a blue-stained chromosome.

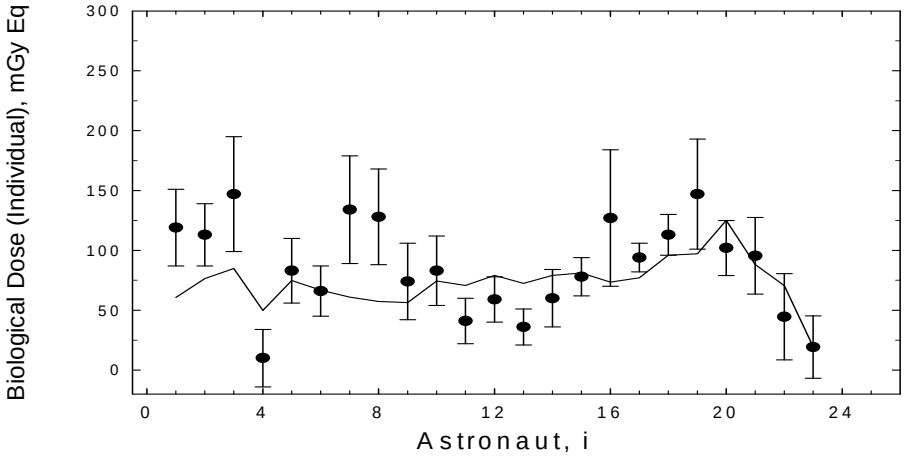


As monocentric chromosome aberrations do not impose mechanistic interference with cell division, lymphatic stem cells should be able to produce new lymphocytes containing stable aberrations, and yields of this type of exchange are, therefore, considered to be stable with time and are commonly believed to persist in peripheral blood cells for many years. This indicates that translocations are a more appropriate tool than dicentric analysis for assessing the effect of chronic radiation exposures such as those encountered during long-duration space missions, as well as for assessing radiation doses retrospectively. Background levels of translocations are higher than those of dicentrics; they are known to increase with age, and show considerable variation between individuals, which limits the usefulness of this technique for accidental exposure scenarios Occupational exposure, such as space flight, is distinct from accidental exposure because pre-exposure levels of translocations can be measured accurately, allowing greater sensitivity in biological dose estimations.

NASA has implemented a biodosimetry program that utilizes the FISH chromosome painting technique to assess chromosomal aberrations in all US astronauts who participate in long-duration International Space Station (ISS) missions. Chromosomes are examined in thousands of lymphocyte cells to identify any structural alterations. The increase in the frequency of chromosomal

aberrations is used to estimate the equivalent radiation dose using individual preflight *in vitro* calibration curves (George et al, 2001 and 2005, Yang et al, 1997). For all individuals, the frequency of chromosome damage measured within a month of return from an ISS mission of 3 months or more was higher than their prefight yield, and biodosimetry estimates lay within the range expected from physical dosimetry.

Figure 3. Biological doses for 23 astronauts who participated in long-duration missions of 3 months or more on board the ISS (Cucinotta et al., 2008). The solid line represents the results of a weighted linear regression model for estimating the dose using physical measurements. For the majority of this group, there is a close relationship between these effective dose estimates and the biological dose equivalent. For some individuals there is a significant difference in the biological and physical dose values and it is possible these differences may reflect inter-individual variation in response to radiation exposure.



Using the cancer risk coefficients recommended by the National Council on Radiation Protection and Measurements (NCRP) the dose range listed in figure 3 would correspond to about a 0.5% increase in developing cancer over a lifetime. As chromosome aberrations in peripheral blood lymphocytes are possible biomarkers of cancer risk, chromosome damage data is being used to develop risk-assessment models that can directly project excess health risk incurred by individual crew members without the extrapolation factors inherent in the NCRP modeling method (Durante et al 2001, Cucinotta and Durante 2006). The biological based risk estimates could provide individual risks that take into account sensitivity to radiation and may be more accurate and informative than population based risk estimations.

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