Biomedical Rationale for Cytogenetic Dosimetry

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Radiation effect/Clinical symptom/Biological dosimetry/Risk assessment/Review.

The purpose of this presentation is to initiate the discussions of automated analysis of radiation-induced chromosome aberrations with a consideration of the possible biomedical benefits to be achieved by its successful accomplishment. Biological indicators of radiation effect are considered. The biomedical indications for and usefulness of cytogenetic dosimetry are described, based on past experiences and potential applications of the developing technology.

The implications of this methodology for both individual and population risk assessment are discussed. Both past experiences and potential applications are considered, with examples, including clinically significant radiation accidents involving radiation workers and members of the public; public health applications in the screening and monitoring of actually and potentially exposed population groups; occupational surveillance of special worker subsets and of the general radiation worker population; and scientific usage in epidemiologic studies and laboratory investigations.

INTRODUCTION

As the first speaker at this International Symposium on Automated Analysis of Radiation Induced Chromosome Aberrations, I would like to take the opportunity to thank Dr. Sato, Directors General Matsudaira and Ishida, Mr. Tomita, Professor Fujie and especially Dr. Hayata for all of the work that has gone into its preparation and for all the support which has been given to its implementation. For me the subject of this Symposium, the automated analysis of radiation induced chromosome aberrations, is a major step towards the attainment of a goal that I have been trying to help reach for almost three decades, the utilization of cytogenetic observations to monitor the impact of environmental and occupational exposures to toxic agents on people's health.

I have been wondering what I can tell you usefully at the start of this important scientific meeting because I am not a trained biological scientist or geneticist, as many of you are. Neither am I qualified as a physicist or engineer, as are others of you. I bring only a background in clinical medicine and some experience in radiation health and in the epidemiology of irradiated populations. This limited background thirty years ago led me to assume that I could, with a little bit of research, develop an automated system for radiation-induced chromosome aberration scoring. It was my good fortune to acquire a very talented set of colleagues and advisors over the years such as Drs. Kendall Preston at Perkin Elmer Corporation and later
at Carnegie-Mellon University, Denis Rutovitz and Jim Piper at the Medical Research Council's Human Genetics Unit in Edinburgh, Scotland, and David Lloyd at the National Radiological Protection Board (NRPB) at Harwell, England. This has brought us to the point where we have now, thirty years later, actually demonstrated the operation of such a system\textsuperscript{2}. Since my own contribution has been mainly in the area of motivation, I think perhaps that it is appropriate for me to give you my personal view of the rationale for carrying on this work.

I should mention, in particular, my own personal experiences in the period from 1954 to 1957 in Hiroshima at the Atomic Bomb Casualty Commission (ABCC), now the Radiation Effects Research Foundation (RERF). At that time an individualized physical dose estimate for each A-bomb survivor was a goal, not a feasible reality. It was the biologic information about the exposed subjects that we worked with that provided our main means to test our crude dose assessments by distance from the bomb detonation point. The aim was to link such a dose assessment with the effects studies that we were carrying on to develop a prediction model for late radiation effects on which to base radiation protection guide-lines, and to understand radiation risks better.

The potential applications of biologic radiation dosimetry, then, are several-fold: an indicator of physical dose; a predictor of the health effects and a method for understanding radiobiologic mechanisms at the cell, organ and organism levels. To initiate our discussion of these, it is necessary to consider the biological effects of radiation exposure.

**BIOLOGICAL INDICATORS OF RADIATION EXPOSURE**

The effects of human radiation exposure can be subdivided into non-stochastic or deterministic\textsuperscript{3} ones, and stochastic ones. The former means effects that have a threshold dose level above which they are seen. These include many of the early biological effects of acute radiation overexposure. The other large category is the stochastic one, in which the probability of occurrence is the variable that depends on dose, and there is no threshold below which the effect may not occur. Cancer and genetic damage are the predominant effects of concern in this category.

Biological predictors of health effects are very useful in both situations. They can improve the diagnosis and treatment of acute radiation injury, and, in chronic exposure situations, they can be used both to estimate the exposure retrospectively and to help anticipate the occurrence of late effects.

Major radiation accidents have given us our information about the acute radiation injury syndromes\textsuperscript{4}. Over the period since the beginning of the atomic era until July, 1991, some 340 accidents have been recorded worldwide\textsuperscript{5}. They have involved about 132,000 people, including about 131,000 in accidentally radionuclide-contaminated areas in the USSR, Mexico, and Brazil. The number of radiation-associated fatalities, 105 cases over the forty-seven years, is relatively small. Indeed, there are few new major industries or important fields of human endeavor that over their early decades have had such a low frequency of fatalities. Nevertheless, we must be prepared to deal with those significant radiation overexposures that do occur.
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The chief problems from the clinical standpoint that are caused by acute radiation overexposure are the acute radiation syndrome or local tissue damage, and, often, the combination of both. Acute radiation injury may also occur without, or in combination with, radionuclide contamination of various kinds. We have also learned that the psychological stress associated with anxiety about radiation injury is truly another major radiation medical problem⁶. It may generate sufficient health impairment to produce signs, symptoms and even disability as can other severe anxiety reactions. Its management, or better yet prevention, must be considered seriously in planning how to deal with radiation overexposure situations.

The acute radiation syndrome⁴,⁷–¹¹ has a number of signs and symptoms that are generally recognizable, such as the early or prodromal symptoms of nausea and vomiting. An increasing occurrence of nausea and vomiting can be expected as the magnitude of exposure increases.

In addition, the damage to the hematopoietic system is reflected by consistent, dose-related changes in the circulating level of various blood cell lines. These are quantifiable² and their determination has already been automated. These phenomena provide the basis for an early appraisal of the degree of clinical injury to anticipate. Table I¹³ presents an early assessment scheme based on such observations.

There are also other biological dosimetric endpoints available, traditional quantitative clinical observations that are not usually given that label, but which in fact are dosimeters.

Table I. Preliminary Evaluation of Acute Radiation Injury Following Overexposure
(from Wald 1992)

**EVALUATION PROCEDURES**
1. Observe and record time of onset of clinical signs and symptoms
2. Perform daily blood count

**FINDINGS**
- Nausea, vomiting, diarrhea within minutes. Ataxia, disorientation, shock, coma in minutes to hours
- Nausea and/or vomiting and some blood count derangement in 2 days
- Marked leucocyte and lymphocyte count derangement in 3 days
- Diarrhea within 4 days and marked platelet derangement within 6 to 9 days

**POTENTIAL OUTCOME**
- Neurovascular Syndrome
- Minor Hematologic Syndrome
- Major Hematologic Syndrome
- Gastrointestinal Syndrome

Among these are changes in body temperature and skin color, and loss of hair. Changes in pertinent tissues, such as the cellular population of the bone marrow that shows a dramatic drop after significant exposure, can also assessed quantitatively. These are useful predictive assays which are related to the magnitude of exposure.

When we put these endpoints together, we have a kind of biological dosimetry system, albeit a crude one, as shown in Table II¹³. Prodromal symptoms, such as vomiting, occur with
Table II. Early Radiation Injury Evaluation Procedures and Their Results in Relation to Time and Magnitude of Radiation Exposure (from Wald 1992)

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>FINDING</th>
<th>TIME OF ONSET</th>
<th>APPROX. MINIMUM EXPOSURE REQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Nausea, vomiting</td>
<td>Within 48 hours</td>
<td>1.5 Gy</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Erythema</td>
<td>Within hours-days</td>
<td>3.0 Gy</td>
</tr>
<tr>
<td>Blood count and differential</td>
<td>Lymphocytes&lt;1,000/mm³</td>
<td>Within 24-48 hours</td>
<td>1.0 Gy</td>
</tr>
<tr>
<td>Chromosome analysis</td>
<td>Dicentrics, rings, and/or fragments</td>
<td>Within hours</td>
<td>0.10 Gy</td>
</tr>
</tbody>
</table>

an exposure of over 1 or 1.5 Gy. About fifty percent of people exposed to 1.75 Gy will show this sign. These also include erythema at about 3 Gy or over, depending on the particular radiation energies involved. Epilation is a confirmatory finding, occurring after about two to three weeks, early enough to be of value in planning the medical management of the subsequent stage of clinical deterioration of the patient.

The very radiosensitive lymphocyte system is another valuable injury guide in which over 1 Gy will produce a definite effect: a promptly falling count below 1,000 cells per cubic millimeter. There are also scoring systems for evaluating the hematological consequences as dosimeters and prognostic indicators of outcome. One we developed in 1959 has continued to find usage (eg., Bavertock and Ash 1983). More recently Fleidner in Germany and Baranov in the USSR have reported their more sophisticated methods along this line.

The advent of a practical method for studying the chromosomes of peripheral blood lymphocytes in 1960 made cytogenetic analysis another option for assessing radiation exposure and its health impact. In 1962, Bender and Gooch first utilized the well-known clastogenic effect of radiation in the evaluation of a radiation accident patient. This application was very helpful in dealing with occupational incidents involving possible radiation overexposure despite it being labor-intensive, slow and costly because of the large number of metaphase cells necessary to study for statistically significant results. In addition to providing a dose estimate in relatively uniform whole-body exposures to low linear energy transfer (LET) radiations from gamma or X-ray sources, it made possible the recognition of non-uniform low LET exposures, and of high LET exposure because of the resultant aberration "over-dispersion", i.e., an excess of cells with multiple aberrations, deviating from Poisson distribution.

Other approaches to the assessment of chromosomal damage have been the micronucleus and sister chromatid exchange analyses. Other speakers will discuss the former method, which has some potential applicability but there are also some major uncertainties to be resolved. The latter method does not appear relevant to the assessment of radiation-induced damage except possibly in special situations such as chronic tritiated water incorporation. It would appear that there is great potential for improvement of radiation dosimetry by cytogenetic aberration or micronucleus scoring through the use of automated processing. There will be
papers on this subject by experts that follow on the program.

For completeness, we should recall that the usage of biochemical endpoints, enzyme changes in particular, and physical measurements such as Nuclear Magnetic Resonance (NMR) or Electronic Spin Resonance (ESR) have been proposed or are under development\textsuperscript{24,25}. None of these are currently practical systems for the emergency evaluation of individuals or populations, or for prospective or retrospective epidemiologic studies.

Having reviewed some of the biomedical effects of radiation overexposure and the resultant endpoints that might be useful in assessing the magnitude of an accidental exposure and its potential prompt or delayed clinical sequelae, we can examine some experiences in the application of these endpoints to the care of actual individuals or populations.

**INDIVIDUAL ACCIDENT DOSIMETRY**

An accident that involved three workers (designated Patients A, B and C hereafter) using an industrial Van der Graaf accelerator can serve as an example of this use of biological dosimetry. A number of aspects of this accident already have been reported\textsuperscript{26–29} so I will focus only on the dosimetric considerations.

Suspicion of a malfunction in the accelerator target cooling system resulted in processing of the film-badge personal dosimeters of the workers, all worn at the waist, but no overexposure was expected in view of the automatic safety features of the accelerator. Early non-specific prodromal symptoms of nausea and vomiting in two of the workers resulted in medical surveillance but these subsided in 24 hours and were attributed to an intestinal virus infection and/or ozone inhalation. Only when the badge reports of 4.85, 6.82 and 1.10 Gy for patients A, B, and C were received at about 56 hours post-exposure was serious consideration given to radiation exposure as a diagnostic possibility. The workers still felt that this was a technical impossibility.

To resolve the exposure uncertainty, we used the signs and symptoms that the workers manifested. Erythema and conjunctivitis were detectable in patient A within 72 hours after the exposure. This gave us an indication of the minimum physical dose since at least about 3 Gy of low energy gamma or x-ray are needed to produce them. Epilation was a clear confirmatory indicator that the exposure to the head was at least 3 Gy when it became evident in this patient about two and a half weeks later.

Next, we turned to the clinical laboratory data. Hematologic tests showed a sharp fall in absolute lymphocytes on the first blood count, confirming that a significant exposure had taken place. There were also very definite changes in granulocyte levels and bone marrow samples of patients A and B. The granulocyte fall actually reached zero at its low point 30 days post-exposure in patient B.

Patient A had even more dramatic early hematologic changes until we interrupted them with a bone marrow transplant from his identical twin brother performed on the 9th post-exposure day. His consequent hematologic recovery began 19 days after the exposure.

The film badges of patients A and B, both worn at the waist, were reanalyzed because the
badges were not designed for such high levels of exposures. They were both corrected to 5.4 Gy. In addition, dose reconstruction was necessary because the exposures were probably not uniform over the whole body in view of the downward direction of the accelerator beam and the fact that patients A and B had their hands at the accelerator target area for varying lengths of time. This was not fully complete until three weeks postexposure, and confirmed that the exposure was nonuniform. The dose rates ranged from 1 Gy per minute at the head level to 50 Gy per minute at the place where hands touched the area of the accelerator target. This led to a revision of the physical dosimetry to adjust for nonuniform distribution. It was determined that the mean midline exposure of patient A was about 6 Gy, exceeding patient B's estimated 3 Gy by about a factor of two despite the same readings of the film badges worn at the waist.

The medical history, physical examinations and routine laboratory tests were thus used as a clinical biologic dosimetry system on which to base necessary diagnostic and prospective treatment decisions, as shown in Table II. On the other hand, the final physical dosimetry data were not available for about three weeks after the exposure, so they played more of a confirmatory role in managing the clinical problem.

We also applied the then rather novel technique of cytogenetic dosimetry for confirmation of our clinical impression, with the help of Dr. Michael Bender, then at Oak Ridge National Laboratory. The chromosome damage in peripheral blood lymphocytes was assessed by fragment (for deletions), ring and dicentric scoring. The exposures for patients A and B based on deletions were 4.5, and 3.4 Gy, while the ring and dicentric estimates were 11.8, and 6.3 Gy. The nonuniformity of the exposure was further confirmed by the finding that the dose estimates based on the two hit phenomena, i.e. dicentrics and rings, were about twice that of those based on the single hit events, i.e., deletions. This had an important influence on our treatment planning.

The diagnostic and prognostic information provided by cytogenetic dosimetry in patients with potential acute radiation overexposure is available in the U.S. in a few clinical and research cytogenetic laboratories, although very labor intensive and therefore costly. This has been satisfactory to deal with the limited number of such clinical patients but presents difficulties when one wants to apply it in occupational monitoring or epidemiologic population studies.

The Chernobyl accident in 1986 provided additional experience with the problems of applying cytogenetic testing a large number of acute radiation syndrome patients. About five hundred patients were simultaneously evaluated in Kiev and Moscow\(^{30}\). Over 200 were confirmed as having acute radiation syndrome with a need for subsequent treatment. In a remarkable performance by the Soviet medical system, it was able to muster the resources needed to carry out the hematologic, cytogenetic and other biomedical studies that served as the primary dosimetric indicators for triage, prognosis and clinical management.

Cytogenetic studies were performed in 154 of the patients within the first few weeks\(^{30,31}\) and the various aberrations were recorded. These biologic data were a major part of the biological dosimetry used in making difficult clinical management decisions since there was no physical dosimetry available for these patients.

To summarize thus far, a set of biological dosimetry tests listed in Table II have been described. They give us pertinent information within time constraints indicated in the table.
It is possible, therefore, to compile a lot of useful biologic dosimetric information in 48 to 72 hours after an accident involving potential high radiation exposure for a limited number of individuals.

POPULATION DOSIMETRY

What is the role of cytogenetic dosimetry in dealing with large populations? The Three Mile Island Nuclear Power Station Unit 2 (TMI-2) accident in 1979\textsuperscript{32} provided us with an early indication of both the difficulties and potential value of performing cytogenetic studies of large possibly irradiated populations. There were some 30,000 people living within five miles of the plant.

There were some major difficulties in communication to the public. Major discrepancies occurred between the alarming newspaper and television reports that people were seeing in the TMI area at the same time as the electric utility that operated the plant and various government agencies were saying that everything was under control. This produced anxiety that was disproportionately high when compared to the actual estimates of any expected effects based on the quantities of radionuclides released. No acute health effects and less than one case of either cancer or genetic defects were predicted from the very small amount of radioactivity released\textsuperscript{33}, but the population had difficulty accepting this information\textsuperscript{34–36}.

The Commonwealth of Pennsylvania was ready to fund our laboratory to do cytogenetic tests on this population because of the uncertainties in the physical monitoring. The other major indication for the testing was the psychological stress, the anxiety and concern of the population in the area that they and/or their families were overexposed to and harmed by radiation. Unfortunately, when we considered the labor, time and cost to generate adequate information for early use by the then current methodology without abandoning the ongoing responsibilities of our cytogenetics laboratory, it was not possible to proceed with the project. However, whole body radiation counts were offered to the public and some 760 persons did avail themselves of this assessment opportunity\textsuperscript{37}.

As anticipated, the behavioral studies are the only TMI follow-up studies that have shown any positive results thus far. Signs of depression were found to be increased in married women with children in particular\textsuperscript{38}. There were also subsequent increased behavioral problems in the children\textsuperscript{39}. In addition, in some of the area individuals, the signs of radiation anxiety and stress are easily reawakened, as evidenced by additional studies\textsuperscript{40} at the time the neighboring and undamaged nuclear plant, TMI Unit 1, was restarted in 1985 for the first time since the accident. It could have been very helpful to be able to do cytogenetic tests to reassure people who were very skeptical about what the government and the plant operators were telling them.

The Chernobyl accident, in addition to its toll of acute radiation injury patients, involved the rest of the population in the area and elsewhere because of the radioactivity released from the reactor core. About forty-five thousand people lived in Pripyat, 5 mile from the plant. They were evacuated by about 40 hours after the onset of the accident. There were rural towns and farm communities within a 30 kilometer circle around the plant, some 90,000 inhabitants of
which were evacuated as well. Others, at greater distances, are still inhabited despite non-uniformly distributed detectable low level contamination. These populations could benefit by biologic monitoring because the dosimetry by physical means is rather difficult and uncertain due to nonuniform local environmental contamination that can also enter the food chain.

Some 600,000 people were in the register of people whose health status is to be followed as of three years ago\textsuperscript{41}. These include plant workers, evacuees and the group of so-called “liquidators”, i.e., the clean-up or mitigation workers in the 30 kilometer evacuated zone since then. This is a very large number of people and the technology with which to carry out the cytogenetic assessment of these intermittent or continuous and, hopefully, low dose exposures on that large a scale does not yet exist.

An accident in Goiania, Brazil\textsuperscript{42}, was another example of relatively large scale contamination of the environment but involved a more localized population. In this city of 1 million people, some 112,000 were monitored in order to identify those externally irradiated and/or contaminated externally and/or internally from a cesium-137 radiologic therapy source that was opened through ignorance. The cesium-137 was distributed in many bizarre ways to a large number of people. The contamination assessment narrowed down to 249 people of whom four died of the radiation effects.

Here again, there was a very large number of people to be managed and monitored all at about the same time. The limitations of cytogenetic methodology and resources again precluded the use of this technique for total population screening. Cytogenetic studies were eventually performed for 110 individuals who could have been exposed to doses higher than about 0.1 Gy, including among them about 60 with internal cesium-137 contamination. Of the total, 25 were done in the first week after the problem was recognized, 50 in the next 4 weeks and the remainder within the following month\textsuperscript{43}. It would have been even more useful to be able to distinguish those members of the involved population with biologically significant exposure earlier.

Next let us consider the A-Bomb survivor populations. The admirable and extensive cytogenetic work done in Japan over many years by Bloom, Awa, Sasaki, Ishihara, Sofuni, Ohtaki and many others, have been well summarized (eg., Awa 1974, 1990\textsuperscript{44,45}). They deal with cytogenetic dosimetry applied to the study of events long past. One conclusion from this work is that in studies that are initiated many years or decades after exposure, the stable aberration, such as translocations and inversions, become the important endpoint. This is because the unstable ones, such as dicentrics, rings and acentric fragments, as their name implies, tend to disappear from the population available for study because of resultant cell replication difficulties. The stable aberrations are more difficult to score, whether in routine Giemsa or G-banded preparations, or through chromosome painting, of which we will hear more at this symposium. The automating of scoring needed to apply this endpoint in cytogenetic dosimetry to populations has not yet been developed except for automated metaphase finding and karyotyping.

Another important aspect of these studies relates to the changes in the relationship of the respective Hiroshima and Nagasaki dose-response curves for chromosome aberration to each other over the years. There was a divergence of the Nagasaki dose-response relationship from
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that of Hiroshima using the tentative 1965 dosimetry (T65D) for each individual. This was explained as being due to the greater neutron component to the Hiroshima weapon yield. A revision of the dosimetry was carried out subsequently, and the 1986 dosimetry system (DS86) replaced T65D. A closer correspondence of the dose-response curves resulted.

The revision of the A-Bomb survivors’ dosimetry was a major factor in the revision of radiation risk estimates in our U.S. National Research Council’s BEIR V Committee report and in the International Commission on Radiological Protection’s ICRP60 reports that are widely used as the basis for radiation protection regulations. Both the physical dosimetry and the cytogenetic studies are being done many decades after the actual exposures and, as a result, have large uncertainties. It is, therefore, important that we should also use other biodosimetric methods to help validate the dose estimates.

The possibility is being approached. One radiogenic biological endpoint being restudied is epilation. The chromosome aberration frequency of the patients with a history of post-A-bomb epilation was compared to the aberration frequency of the patients given the same dose assignment who did not epilate after the A-bomb exposure. It became evident that the cytogenetic effect of a given dose was significantly greater in those who epilated. The authors consider that although differences in radiosensitivity may be involved, the difference in dose-response is most likely due to random dosimetry errors of 45% to 50% in the DS86 dosimetry.

There are other comparisons which are coming into use now, such as the corellations among the cytogenetic, glykophoryin-A and HPRT mutation analyses in the A-Bomb survivors. It is very important to utilize all of the available study techniques that have good potential for detecting mutational radiation effects, more about which you will hear at this symposium, since most of our current radiation risk predictions for the occurrence of radiation-induced cancer on which radiation protection regulations for radiation workers and the public are based from the ongoing assessment of the Japanese survivor population.

There are some other populations can be studied usefully for improved risk estimation. One such study in China involved a very stable population in which a comparison was made of those living in an area with an average natural radiation background level and those living in a similar area but with a background almost three times higher. The thyroid gland is highly radiosensitive so the presence of thyroid nodules was determined as well as bytogenetic changes. The population in the high exposure area did not have an increase in thyroid nodularity but did have an increased frequency of unstable and stable chromosome aberrations. More radiobiological information could be learned through the use of the newer biologic methods about the effects of radiation delivered over a long time at a constant, very low dose rate.

Another set of populations, the occupational exposed radiation workers, receives chronic and/or intermittent exposure at varying dose rates. Many years ago, Norman and coworkers and Court Brown and colleagues pointed out that groups of radiation workers showed an increasing frequency of dicentric chromosomes parallelling the increasing cumulative exposure that these workers acquired working within permissible occupational radiation limits over increasing numbers of years.

More recent studies of nuclear shipyard workers and of National Radiological Protection Board employees have confirmed that exposure within occupationally permissible limits over
many years can result in an increased incidence of chromosome aberrations with a linear dose-response relationship. Although these studies have shown the feasibility of detecting permissible occupational exposure in worker populations, the very large numbers of cells that must be analyzed at these very low levels of exposure have limited these studies to groups of workers rather than to individuals.

Thus far, this requirement has precluded the use of cytogenetic methodology for another long-sought goal, biologic occupational monitoring$^{56}$, with the objective of detecting workers who, for reasons of individual increased radiosensitivity or because of non-uniform or internal radiation exposure that may not be detected by their personal physical dosimetry devices, have greater than expected chromosome aberration frequencies. If appropriate technology were available, consideration could be given to supplementing the time-honored maximum permissible occupational exposure limit with a maximum permissible cytogenetic aberration limit as a more personalized indicator of cumulative environmental stress and response. This could then be evaluated as a potentially better predictor of the risk of late health effects than the physical measurement of occupational radiation exposures. Automated cytogenetic aberration scoring or the automated use of other biologic endpoints could make the evaluation of this possibility feasible in the future. It is increasingly important to enhance the capability to use cytogenetic dosimetry as a technique for monitoring the effects of worker exposures because there now are a growing number of people who have been working for their entire occupational lifetime in the radiation industries.

Such technological advances could also offer the potential for detecting individuals and families that may be carriers of genetic abnormalities that are associated with increased chromosomal breakage and an increased likelihood of cancer as well as, in some instances, increased radiosensitivity$^{57}$. Chromosomal radiosensitivity assays have now been reported to show a higher frequency of induced dicentrics in Down syndrome and, more recently, in Alzheimer’s disease patients$^{58}$, while radiation-enhanced chromatid damage has been used to identify cancer-prone gene carriers in families with ataxia telangetasia, hereditary cutaneous malignant melanoma and the precursor dysplastic nevus syndrome, or xeroderma pigmentosum$^{59}$.

In summary, it is evident that there are many clinical, epidemiologic and research applications awaiting the automated analysis of radiation-induced chromosome aberrations. There is a good biomedical rationale to go on with the work. Let us, therefore, participate in the presentations and discussions that follow in this valuable symposium, and in the further progress that they stimulate.

REFERENCES

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