Retrospective Dose Assessment

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Introduction

Radiation dose reconstruction has become a significant environmental sciences specialty over the past decade. Models to integrate limited radiological measurements have been developed and are being validated and improved. For external exposures, our main tools are computer simulations of radiation output from a "source term", be it the A-bombs dropped on Japan, or a hospital fluoroscope. Validation without actually duplicating the exposure conditions leaves a level of uncertainty that is difficult to reduce. The second major class of radiation dose reconstructions relates to those doses absorbed as a consequence of radionuclide intake. Here too, uncertainties exist as to the exact "dosage" quantity and quality and pharmacokinetic behavior in an individual or population are usually not available. I wish to restrict my remarks to this latter case, but also realize that some of what I have to say may be germane to external exposure problems.

Simply stated, my thesis is that the reconstruction of doses from the outside inward, can be assisted by personal biological radiation dosimetry from the inside out. I believe that the case can be made for the fact that the deficiencies and limitations of both sets of tools, environmental and biological dosimetry, are in different dimensions and that the strengths of one approach can assist in reducing the weaknesses in the other. Ideally, an integration of biological and environmental dosimetry for the same case will be synergistic and the resultant "collective" uncertainty will be minimized. This is particularly true of very low doses, where the sensitivity and detection limits of available techniques are stretched to their utmost. For radionuclide-related dose reconstruction, environmental measurements of concentrations and pathways infrequently sufficient to determine a biological source term, the quantity potentially taken in by the individual of population. Adding the appropriate biological, demographic, and environmental factors generates the consequent dose estimate. In the best of all worlds, the findings might be confirmed by actually measuring excreta, body-burdens, and/or biological indicators of radiation damage. We rarely have been able to realize this ideal, because those exposed may have had doses that were below the sensitivity threshold for the available techniques.

I would like to review some of these techniques and present an argument for increased research and development of biological indicators which may provide more sensitive output. To keep this in perspective, I feel that there is room for improvement and advances in the environmental tools as well as for biological dosimeters. A host of sophisticated computer programs now provide a platform for rapid integration of data and integrated output of results. Atmospheric and environmental transport models have continued their evolution to powerful tools.

Remote sensing of biological indicators, such as infrared reflection and emission signatures of radiation damaged plants are now available. Aerial surveys, yielding planar spatial isoconcentrationn gradients of surface contamination are being improved by integrating global-positioning-systems with focal emission rate data. Faster processing and more sensitive, stable detectors are also providing improvements. On the ground, improved sampling techniques, provide concentration gradients and temporal and spatial profiles important for reconstructing prior situations. Thermoluminescent dosimetry of stable signals form radiation exposed geologic and biologic samples add to our armament. All these techniques present opportunities for dynamic improvement. Added to these tools are the retrospective, historic description and documentation of events and measurements of past exposure related information. At times, I am not too certain if there is adequate support and commitment for the future development activities. I add my personal plea for a more integrated international program to improve sensitivity of techniques, to calibrate and "certify" the techniques and to explore and develop new methods.

Biological Dosimeters

The object of this overview is to indicate some important roles for biological indicators of radiation exposure in our overall planning for modern radiation retrospective dosimetry. These are either bioassays, direct physical measurements of radiation and radioactivity, or they are biological signals which are derived from living systems which record radiation effects.

Biological assays of radioactivity are simply collections of excreta from body burdens, the data from which when input to pharmacokinetic models provide and indirect estimate of the body burden and hence the associated radiation dose. This is particularly important for alpha emitting radionuclides whose emanations are too difficult or impossible to detect in-vivo. Whole body and partial body counting techniques are especially sensitive for body burdens of gamma-emitting radionuclides. Energetic beta-emitters can be assayed using bremmstrahlung counting and appropriate standards. (An important contribution from Chelyabinsk, Russia will illustrate this tool). Post mortem tissue sampling, and in some cases, tissue biopsy, (e.g. tooth), can also provide direct input into body burden estimation.

A renewed interest has developed for the use of electron spin resonance of biological crystals which had received radiation doses. Because of the long stability of the signal in exposed crystals the technique has even been applied to dating of mastodon tusks, using the integrated natural background radiation signal over many thousand years. More practically, it has been used to measure the absorbed dose signal from the jaw of a survivor of the a-bombing of Hiroshima 39 years ago. The crude device had poor sensitivity, (i.e. 1 Gy), but did demonstrate the feasibility of the method. For small chips of tooth enamel, a sensitivity of about 0.1 Gy is reported and a ten-fold improvement is quite possible. (We shall hear more of this in today's Symposium).

I would like to make a plea here for a concentrated effort to truly exploit this technique to its limit, to effectively engineer and develop both an in-vivo and an in-vitro methodology that is internationally calibrated and accepted. My journeys through this technique over the past eight years have proven to me that many well-meaning scientists working in competition have not yet assembled the critical mass needed to achieve this goal in a reasonable time. For the dose reconstructions planned, as well as for accident management needs, there is no reason to continue in present manner. I view this techniques as a biological dosimeter as useful as the thermoluminescent dosimetry as proven to be for personal and environmental dose documentation. This is one of my challenges to you.

Cellular markers or indirect indicators of radiation dose are either cytologic indicators or variations on measurement of somatic gene mutations. The advances in cell and molecular biology have not in my opinion carried adequately over to the arena of biological dosimetry. Years ago we were promised an automated **chromosome aberration scoring** device. We are still waiting for a dependable karyotype scoring device. For the most part, the scoring of chromosomal aberrations is still done manually and tediously as it was some three decades ago. Where is the application of modern pattern recognition, so well developed for space applications, but absent in microscopic assays? There have been a few heroic attempts to solve the problem, but it appears that there is no truly integrated biological-engineering heavy attack on the problem. Since the greatest interest is in stable chromosome translocation scoring, the least plentiful aberration, it is all the more imperative to push this technology as far forward as is possible. In this case, sensitivity and accuracy is a function of the sheer number of cells that are scanned, and is limited to the visual fatigue index of the scoring technician. This is another serious challenge for us to address.

The **micronuclei test** is very useful, accurate and simple. It has a major drawback in that it does not distinguish between dividing and non-dividing cells; thus as an unstable aberration assay it is limited to very short times after exposure and is not very helpful in long term retrospective dosimetry.

A newer cytogenetic tool to identify chromosomal translocations has now been developed. The use of **fluorescent in-situ hybridization** now appears as one of the more powerful techniques for identifying stable damage to chromosomes from radiation. The technique is complex and at present limited to a few laboratories. It is costly and it remains to be seen if some automated modification will be available which can increase its applicability and sensitivity to detect small radiation doses. It has sufficient promise though, that I would encourage a quantum increase of multi-disciplinary expertise focussed on this assay, especially in determining its ultimate sensitivity. This is my third challenge.

For several years we have been presented with an array of somatic gene mutation techniques. One that has received much attention recently is the **glycophorin-A assay**, using a fluorescent labeled monoclonal antibody to the protein

and measuring the loss of a red cell allele in irradiated people. It is purported to be a very stable indicator, with lifelong persistence. I am not enough of a biochemist to go into great detail, but I am concerned that the technique has severe limitations as a radiation biodosimeter. It does not appear very reproducible in the same individual, even though millions of red cells are measured in the assay. There seems to be very great variability among individuals exposed to the same dose, and there has not yet been a careful calibration using persons with known exposures. It is simple, relatively cheap and potentially useful if it can be calibrated and validated.

As with the micronuclei test mentioned above, the **HPRT - mutation assay,** (hypoxanthine phosphoribosyl transferase mutations in T-lymphocytes), is limited to very short times after exposure; it's "signal" faded rapidly. Another assay, the **HLA-A,** (human leukocyte antigen A assay), is tedious, insensitive and not promising at this time. The **beta globulin test** likewise offers some promise, but it is too early to state if this fluorescent antibody indicator of a single base change in hemoglobin can provide a practical tool. There may be other useful techniques in various stages of development.

Individual Biological Dosimetry: an Integral Part of Radiation Dose Reconstruction

What is advocated here is the full utilization of these biomarkers as integral elements in future radiation dose reconstructions. What I have seen thus far is the occasional use of one or more assays, more as an afterthought than an integral part of the protocol. The reason for this which is usually put forth, is that the techniques are too expensive and technology intensive and with insufficient radiation reliability or sensitivity. However the limitations of environmental radiation dose reconstruction also entail significant uncertainties about the variables used in modeling, no matter how sophisticated the tool.

While we are improving the validation and calibration of these models, why not also put in the effort to render the biological tools more sensitive and reproducible? Incorporating statistically appropriate individual measurements in the reconstruction matrix can add a powerful dimension to our efforts at dose reconstruction. I envision a time in the near future when there may be a convergence of these two approaches with a resultant synergy of action that produces dose reconstructions with minimal uncertainty and maximal credibility. I can see where the strengths of each technology can assist in reducing the weakness of the other, to help us answer important questions about prior radiation exposures. Major resources are expended on epidemiology studies, with great emphasis on confounding factors, on subtracting natural disease rates from the subject population, etc. However all this emphasis on reducing uncertainties on the "ordinate" of the relationship, must be accompanied by an equal dedication to minimizing uncertainties about dose. Population estimates based solely on broad environmental models, while sensitive, can only be verified by use of individual measurements. Despite 30 years of work, individual doses in survivors of the

atomic bombing of Japan, still pose large levels of uncertainty. New biological dosimetry is helping to reduce the uncertainty; and so it should in the other populations at risk from prior exposure. That is my final challenge to you.

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