Collective Radiation Biodosimetry for Dose Reconstruction of Acute Accidental Exposures: A Review

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Quantification of the biologically relevant dose is required to establish cause and effect between radiation detriment or burden and important biological outcomes. Most epidemiologic studies of unanticipated radiation exposure fail to establish cause and effect because researchers have not been able to construct a valid quantification of dose for the exposed population. However, no one biodosimetric technique (biophysical or biological) meets all the requirements of an ideal dosimeter. This paper reviews how the collection of biodosimetric data for victims of radiation accidents can be used to create a dosimetric "gold standard." Particular emphasis is placed on the use of electron spin resonance, a standard for radiation accident dosimetry. As an example of this technique, a review will be presented of a previously reported study of an individual exposed to a ^{60}Co sterilization source. — *Environ Health Perspect* 105(Suppl 6):1397–1402 (1997)

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Introduction

Collective Radiation Biodosimetry

Acute radiation accident dosimetry provides the best means of estimating radiation risk by extrapolating its effects to lower doses. Determination of the radiation exposure history of the general population has become increasingly important in the study of the effects of low-level radiation. The effects of low radiation levels are deduced by extrapolation of the effects at medium radiation levels, because data for low levels are difficult to obtain (*1–3*). Alternatively, acute radiation accident dosimetry presently provides the best means of estimating radiation risk by extrapolating its effects to lower doses. In addition, it can provide a means of triage for determining therapeutic strategies and prognoses. Finally, radiation accident dosimetry can be of forensic value in postmortem investigations and can aid our understanding of the accident process.

Radiation doses and distribution for acute exposures are estimated by physical measurements using electron spin resonance (ESR), biologic dosimetry, and computer simulation. ESR is used to detect free electrons produced by radiation in dental enamel and clothing of a victim and is a measure of absorbed dose (*4–18*).

Biological techniques provide a measure of the biologically relevant dose and involve the study of chromosome aberrations in blood lymphocytes and the kinetics of granulocyte and lymphocyte production after the exposure to radiation (*19–26*).

A major goal of radiation dosimetry is to establish causality in areas such as the prediction of health effects, risk assessment, and radiation protection. A major obstacle to this goal is the difficulty in establishing dose–response relationships for individuals or populations (*27*). There are difficulties in reconstructing a valid biologically relevant dose and in assessing appropriate outcomes. Most biological indicators are not measures of accumulated doses but indications of biologically significant doses. Further, biological dosimetry is not without its limitations. It is transient, technically difficult, and of limited sensitivity (*25*).

ESR in dental enamel is a good surrogate of absorbed dose. However, it provides no information about biological impact; it is not a direct measure of whole-body dose; and it is subject to confounding factors such as the effect of ingested β-emitters (*28–30*). The problem of intersample variability in sensitivity to radiation must also be addressed (*31*). Finally, ESR is limited in sensitivity and requires a large array of laboratory equipment and extracted teeth if dental enamel is to be used.

There are abundant reports in the scientific literature that present reasonable results for absorbed and biologically relevant doses associated with radiation accidents. In each case the strengths and weaknesses of the techniques used are exploited. Thus, it may be most reasonable to establish truth in radiation dosimetry through a consensus of the various techniques commonly in use, i.e., establish dosimetric truth by using a collective of biodosimetric techniques (*22,25*).

Biophysical Dosimetry Using Electron Spin Resonance in Biological Hydroxyapatites

History. Electron spin resonance is a physical technique for monitoring the presence of unpaired electrons in matter (*32*). Irradiation of substances by high energy (ionizing) electromagnetic radiation produces these electrons, called free radicals. A long-lived ESR signal was first observed in X-irradiated biologically significant materials such as alanine and bone by Gordy and Shields (*33*) and subsequently studied by Blyumenfel'd and Kalmanson (*34*). ESR signals from hydroxyapatite were then explored more thoroughly by several groups (*4,5*); ESR in irradiated dental enamel was reported by Cole and Silver (*15*).

Dental enamel remains essentially inert after its formation (*35*). Consequently, of all living tissues in the body, only dental enamel can retain indefinitely the history of its radiation exposure. The effect of ionizing radiation on hydroxyapatite crystals of dental enamel is to produce free electrons that can be trapped in defects in the crystal lattice (*36,37*). These trapped electrons have an indefinite lifetime (*38*). ESR can be used to measure the absorption of electromagnetic (microwave) radiation by these free radicals. The magnitude of this absorption is proportional to the number of free radicals and thus gives a measure of absorbed dose (*4,5,7,8,10,39*). A distinct advantage of ESR is that readouts are nondestructive. That is, the radiation history

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Abbreviations used: ESR, electron spin resonance; OSL, optically stimulated luminescence; TL, thermoluminescence.

is not destroyed by ESR measurements, as is the case with thermoluminescence (TL) dosimetry (*40–42*).

The use of ESR in human hard tissues for accident dosimetry was suggested by Swartz (*4*) and then elaborated on by Brady et al. (*43*). Subsequently there were attempts to use ESR for accident dosimetry in investigations of the victims of the Hiroshima and Nagasaki atomic bomb detonations (*8,44*) and of the military participants in nuclear weapons testing (*47*). Investigation into the use of ESR in dental enamel (*9,10,45–47*) and in alanine (*12,14,48*) as a means of radiation accident dosimetry progressed simultaneously in several different research centers.

Studies of the basic nature of the ESR signal from irradiated proteins and biological crystals also proceeded in various laboratories (*6,7,49–52*). Separation of the contributions from diagnostic X-rays and high energy γ rays to the ESR signal in dental enamel and proper account of the mass-energy attenuation coefficient were investigated by Aldrich and Pass (*18*) and then elaborated on by other groups (*53–55*). This separation uses the dependence of attenuation of absorbed dose across the width of a tooth on energy of the incident radiation. When studying the lower range of doses absorbed by the general population, diagnostic radiation becomes a significant contribution to the total accumulated dose.

Limitations of ESR. Although ESR dosimetry is a widely accepted means of rapid and early detection of absorbed radiation doses, it does possess two important disadvantages: limited sensitivity and lack of portability. The low sensitivity exists, primarily, because of the small interaction between the electron magnetic dipole moment and the externally applied magnetic field required to observe the ESR signal. The magnitude of the associated magnetic dipole energy level transitions is proportional to the product of these two quantities and is approximately 10^{-6} that of the readily observable optical transitions in an atom. This weak nature of the electronic energy level splitting in the presence of an external magnetic field necessitates a large number of spins (i.e., large samples) and a large external magnetic field to achieve sufficient signal strength and adequate detection limits.

ESR in dental enamel for radiation dosimetry is further limited in sensitivity because of the presence of a radiation-independent signal that occurs at the same position in the ESR spectrum as the radiation-induced signal and, hence, can mask it. A radiation-independent ESR signal in hydroxyapatite was first studied by Becker (*56*). A radiation-independent signal in dental enamel was identified by Ikeya et al. (*9*) and attributed to the organic content of enamel. Subsequently, Pass and Aldrich (*11*) labeled this the native signal and discovered the dependence of its magnitude on microwave power. For conventional ESR in natural dental enamel, the presence of the native signal limits detection of the radiation-induced signal to 0.5 ± 0.5 Gy.

Pass and Aldrich (*11*) reported that the magnitude of the native ESR signal reaches a plateau, whereas that of the radiation-induced signal continues to increase as the power of the stimulating microwave radiation increases. This selective saturation (*57*) of the native signal with increasing microwave power improved the lower detection limit to approximately 0.3 ± 0.3 Gy (*58*). Subsequently, derivative ESR techniques such as rapid passage (*59,60*) and pulsed ESR (*61*) were developed to exploit this relaxation time dependence of the ESR signal in dental enamel to further improve sensitivity. Separation of the overlying native and radiation-induced ESR spectra has also been studied using electron-nuclear double resonance (*62*).

Further reduction of the influence of the native signal was achieved by thorough deproteination of the enamel sample to remove the protein matrix (*16*). The maximum reduction in the native signal magnitude that can be achieved in this manner is 50%. The inability to completely remove the native signal with deproteination indicates that there is also a contribution to the native signal from unpaired electrons in the inorganic crystalline hydroxyapatite not created by incident radiation. These electrons may reside in energy levels deep within the gap between the valence and conduction bands of the hydroxyapatite (*63*).

With limitations, coherent computer subtraction of the native signal from the experimental ESR spectrum can achieve further improvement in sensitivity (*57*). In this procedure the background signal is simulated by a Lorentzian line (*64*) or a pooled signal from a collection of nonirradiated deciduous teeth. The simulated signal is then coherently subtracted from the experimental ESR signal, which consists of both radiation-independent (native) and radiation-dependent signals.

The result of the above efforts is that, at present, the limit for a detectable dose using ESR in dental enamel is approximately 0.1 Gy, with a standard deviation of 15% (*57*). However, true *in vivo* dosimetry without calibration problems, and detection limits less than 0.1 Gy may require a new technology other than ESR such as optically stimulated luminescence (OSL) in dental enamel recently reported by Godfrey-Smith and Pass (*65*).

The lack of portability and general applicability of ESR in dental enamel for radiation dosimetry exists for two reasons. First, because of the large magnitude of the externally applied magnetic field required to observe the ESR signal, a large array of laboratory equipment is used. Second, the large sample size required (typically 0.1 g) necessitates the use of extracted teeth. There has been only limited success in producing a smaller portable spectrometer for true *in vivo* dosimetry (*66,67*). Such a device would permit monitoring of accumulated radiation doses in the general population and subsequently facilitate direct determination of radiation risk. A technique for enamel sampling and subsequent tooth restoration has been developed in the event such an invasive procedure is warranted (*68*). OSL in dental enamel, however, may make noninvasive *in vivo* dosimetry possible.

Future use of ESR dosimetry may routinely employ substances other than enamel and alanine (*69–71*). Investigations of irradiated foods have also made extensive use of ESR dosimetry (*72,73*). Along with the use of ESR in radiation dosimetry, the use of ESR in geologic dating developed (*39,74*). Consequently, today ESR is a reliable and widely used means of achieving retrospective radiation dosimetry.

Case Study of an Acute Accidental Exposure

The exposed individual in this study entered a γ radiation chamber used for sterilizing medical supplies. The ^{60}Co source (specific activity, 3×10^{16} Bq) had not retracted properly. The total exposure time was estimated at 1 to 2 min at 0.5 m from the source, with the left anterior side slightly closer to the source. This case, presented here as an example of the collective dosimetry technique, was previously reported by Pass et al. (*31*).

Electron Spin Resonance in Dental Enamel

Dental enamel from the accident victim was analyzed by Canadian and Russian laboratories. The Canadian laboratory

(Dalhousie University, Halifax) used the ESR calibration curve technique (*11*) for determining the unknown dose absorbed by the victim's dental enamel. In this method an ESR signal dose–response calibration curve was generated by intentionally irradiating whole teeth from the general population with known doses, in a single increment, from 0.5 to 20 Gy. Using the calibration curve, the ESR signal resulting from an unknown absorbed dose can provide the magnitude of that dose.

The intentional irradiation was done using ^{60}Co 1.25 MeV γ rays from a Theratron 1000 or 6 MeV X-rays from a Therac 6 linear accelerator (Theratronics International Ltd., Kanata, Ontario, Canada) Both these devices administer radiotherapy for treatment of malignancies and are calibrated to give the dose to muscle at the target volume in compliance with the dosimetry protocol established by the American Association of Physicists in Medicine (*75*). Absorbed calibration curve doses to enamel were calculated, using the proper exposure–dose conversion factors for dental enamel, as a function of photon beam energy; these were first calculated and used by this laboratory (*76*).

Account was taken of secondary electronic equilibrium in calculating the absorbed calibration curve doses to the enamel aliquots (*77,78*). In particular, for ^{60}Co γ irradiation with a dose rate in air of 1.84 Gy/min at a 100-cm source-to-object distance, 0.5 cm of "superflab" tissue equivalent (Mick Radio Nuclear Instruments Inc., New York, NY) was placed over the tooth. A plexiglass plate, 2.54-cm thick, was located behind the sample to establish the appropriate backscatter. For 6 MeV X-rays 1.5 cm of tissue equivalent material was used. A detailed description of the steps followed to achieve secondary electronic equilibrium was provided by Shimano et al. (*53*). A thorough account of the irradiation conditions, dosimetry, and normalization procedures used with ESR dosimetry was provided by Schauer et al. (*55*).

Enamel samples for the calibration curve were obtained from teeth extracted in a university clinic in the normal course of dental treatment. After irradiation of a whole tooth, dentin was separated from the overlying enamel by slow grinding with a dental hand drill. Dentin is discernible from enamel because of its yellow color. Clean enamel was then crushed slowly into coarse chips using a ceramic mortar and pestle. A typical sample size was 100 mg.

ESR was performed on these samples using a Varian E-109B ESR spectrometer (Varian Associates, Palo Alto, CA) at room temperature. Signal size was determined from the peak-to-peak measurement of the main signal at g = 2.002 of the first derivative of the microwave absorption spectrum (*10,11*). The Russian laboratory, the Institute of Biophysics in Moscow, used the additive dose technique (*9,39*) with a Bruker 300 ESR X-band spectrometer (Bruker Instruments, Billerica, MA). In this technique the sample being studied is intentionally irradiated in chosen dose increments; the actual sample is used to generate the equivalent of its own calibration curve. An ESR dose–response curve for the sample, at ambient temperatures, is constructed and extrapolated to the dose axis, the intersection of the lines providing the initial, inherent dose. For materials other than dental enamel, such as clothing and finger nails, fragments of the substances were irradiated over an appropriate range of absorbed doses with the ESR responses determined by peak-height measurements and double integration (*71*).

Biological dosimetry used both dynamic parameters and cytogenetics. Dynamic techniques were based on serial determination of the levels of granulocytes and lymphocytes following the accidents. Cytogenetic techniques evaluated the presence or absence of dicentric chromosomes in blood and bone-marrow cells (*79*).

Results of Electron Spin Resonance Measurements

Dose estimates by Russian researchers using computerized accident simulations were consistent with a dose of 12.5 Gy (95% confidence interval: 10 to 15 Gy). Cytogenetic techniques assessing chromosome aberrations in cultured blood lymphocytes indicated a dose range of 9.6 to 11.7 Gy. The dose estimate from blood granulocyte kinetics was 9 to 11 Gy. ESR in clothing material indicated an exposure range of 12 to 18 Gy. The maximum dose was registered at the left anterior chest, while the minimum dose occurred at the right posterior chest (Figure 1). ESR studies of dental enamel in the Canadian laboratory determined the exposure to be 13.7 ± 1.4 Gy, which is in good agreement with the Russian estimates. Table 1 provides a summary of the dosimetry for this radiation accident victim.

The 50% lethal dose to bone marrow in humans is 3 to 4 Gy. Hematopoietic suppression is considered irreversible with doses exceeding 8 Gy. Partial hematopoietic recovery was achieved with the third subject using supportive measures, transfusions, and hematopoietic growth factor but no transplants in a Moscow hematology ward (*80*). The patient died 113 days following the accident from radiation pneumonitis infection secondary to diffuse and focal fibrosis of the lungs.

Discussion

Establishing a Dosimetric "Gold Standard"

External validity for radiation dosimetry would be established with favorable comparison to a verifiable truth. Such a dosimetric gold standard does not exist, although it is required in the study of a cause-and-effect relationship between radiation and the risk of cancer (*27*). In addition, it has been recommended that efforts be made to integrate classical epidemiologic methods with laboratory data from cellular and molecular biology to guide risk estimates for radiation-induced cancer in humans (*81*).

Most biological indicators are not a measure of accumulated dose but an indication of biologically significant dose.

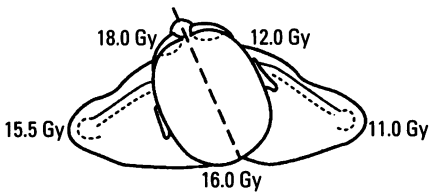

Figure 1. Distribution of absorbed doses around the torso of the victim of a radiation sterilization facility accident. Values were determined by ESR in clothing using the additive-dose technique (*31*).

Table 1. Radiation dosimetry for an irradiation facility accident.[a]

Statistics on patient	Accident date, 1991 Age, 34 Sex, male
Personal dosimeter	None
Simulated dose	12.5 ± 2.5 Gy
ESR/clothing	12 – 18 Gy
ESR/dental enamel	13.5 ± 1.5 Gy [b] 13.7 ± 1.5 Gy [c]
ESR/finger nails[d]	≥ 10 Gy
Blood lymphocyte kinetics[d]	8.5 ± 1.5 Gy
Granulocyte kinetics[d]	10.0 ± 1.0 Gy
Chromosome aberrations[d]	11.0 ± 1.0 Gy
Clinical outcome[b]	Patient died 110 days after accident from radiation pneumonitis

[a]Data from Pass et al. (*31*). [b]Russian laboratory using additive dose technique. [c]Canadian laboratory using calibration curve technique. [d]Data from Baranov et al. (*80*).

Further, biological dosimetry is not without its limitations. ESR in dental enamel may be an integrating dosimeter but is subject to confounding factors such as the effect of ingested β-emitters (*30*) and the intersample variability in sensitivity to radiation (*31*). Thus, it may be most reasonable to establish truth in radiation dosimetry through a consensus of the various techniques commonly in use (*22,25*).

Collective biodosimetric data could, for example, be treated in a manner analogous to that described by Baranov et al. (*79*). In that study, a pooled biological dose was calculated. This correct dose was computed as an average of the collective biological dosimetry, with weights based on variances of the measurements for each technique. In this regard, the present study works toward the goal of collective dosimetry for dose reconstruction (*16,27,29,82,83*). However, comparisons in the scientific literature between biological and physical methods of radiation dosimetry remain infrequent (*80,84–86*).

Some measure of external validity for ESR dosimetry and collective biodosimetry is achieved when there is agreement between them. This is the case for the present study. External validity of ESR is also enhanced when it agrees with the results of other independent dosimetric techniques such as mathematical modeling used for simulation of a radiation accident (*87*) or the planning of radiotherapy treatment (*88*). Agreement between retrospective ESR dosimetry and that from personal dosimeters of radiation accident victims or occupationally exposed individuals also supports external validity but is not often reported (*16,89*).

Internal validity, or consistency, for ESR can be enhanced by establishing agreement between its applications in a given study. For example, the present study has indicated agreement between ESR in the various substances from the victim's person. In particular, ESR in clothing, fingernails, and dental enamel were consistent, even though working with clothing (*90*) and fingernails (*71*) present special difficulties because of signal fading. Further, every investigation with clothing requires individual calibration because of the influence of many factors (e.g., manufacturer, color and dirt present, and sample orientation) on the interaction between radiation and the specimen.

Confounding Factors in Electron Spin Resonance Dosimetry

There is further support in this study for internal validity in the agreement between the calibration curve and additive dose techniques for the large accidental doses studied. However, it was reported by Pass et al. (*31*) that there can be significant variability in the ESR sensitivity of enamel to radiation between teeth of different individuals. This confounding factor cautions against the use of the calibration curve technique.

There are confounding factors affecting ESR dosimetry with dental enamel in addition to the variability in ESR sensitivity discussed above. Consider, for example, the Chernobyl nuclear accident: ^{137}Cs was a significant component in the radioactive plume. The β-particles emitted by this element are the major contributors to internal radiation exposure (*91*). Thus, the β contribution to the ESR signal in dental enamel from ^{137}Cs deposited on the outer surface of the crown of the tooth and internally in dentin may be significant. For nuclear accidents such as that at Chernobyl, assessment of internally deposited β-emitters must be made (*29,30*). Then an appropriate model to account for the β contribution to the ESR signal in dental enamel should be applied (*28*).

A New Biophysical Dosimetry: Optically Stimulated Luminescence

Although there has been limited success in producing a smaller portable ESR spectrometer, ESR is still not suitable for true *in vivo* dosimetry (*66,67*). Optical technology holds the promise of being sensitive, amenable to miniaturization, and noninvasive.

OSL was developed as a means of dating geological sediments (*92–95*). The underlying phenomena for OSL are similar to those of TL and ESR. In OSL the only trapped electrons detected are those that can be freed by absorption of near-visible or visible photons. The first successful detection of time-dependent OSL from γ-irradiated enamel was recently reported by Godfrey-Smith and Pass (*65*). The task now is to lower the detection limit to at least that for ESR (0.1 Gy) and establish a dose–response relationship.

Conclusions

There are many reports in the scientific literature that present reasonable results for absorbed and biologically relevant doses associated with radiation accidents. In each case, the strengths and weaknesses of the techniques used are exploited. However, dosimetric external validity requires some concept of dosimetric truth. Consensus may be the best approximation to this truth. Thus, it is important to accumulate and analyze studies that apply collective dosimetry to analysis of acute radiation exposures or to lower levels of radiation exposures found in occupational and general populations at risk. Further, it would be beneficial to plan a collective dosimetry immediately after an accident has occurred. For the case presented here, however, a collective dosimetry was constructed by combining separately published data.

With the perfection of OSL in dental enamel, development of a noninvasive, integrating biodosimetric technique that is sufficiently sensitive, reliable, specific, convenient, and inexpensive will be closer to realization. With such a device, surveying the general population would be possible. This would facilitate establishing a dosimetric gold standard and making reliable cause-and-effect determinations feasible for exposures to ionizing radiation (*27*).

Designation of the essential clinical or occupational-related outcomes and their assessment would be needed to evaluate the success of a collective dosimetry. Examples of such outcomes are health effects, radiation protection, radiobiological effects, and risk analysis. While requirements of a biodosimeter can be enumerated (*25*), the concept of a successful dosimeter continues to evolve.

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