Paper

Estimate of the Deterministic Neutron RBE for Radiation-induced Pseudo-Pelger Huët Cell Formation

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Abstract—**Using archival peripheral blood slides from radiation accident patients, we have recently described the pseudo-Pelger Huët anomaly (PPHA) in neutrophils as a new radiation-induced biomarker, useful for dosimetry not only immediately after a radiation incident but also potentially helpful as a tool in retrospective dosimetry. In conjunction with the Radiation Accident Registry at the Radiation Emergency Assistance Center/Training Site (REAC/TS), the frequency of PPHA cells has been compared from selected patients in the Y-12 criticality accident in Oak Ridge, TN, in 1958 and from the patient in the 1971 ^{60}Co accident at the USAEC Comparative Animal Research Laboratory (CARL), also in Oak Ridge. Patients A, C, and D in the Y-12 accident are described as having an average dose of 2.53 ± 0.14 Gy gamma + 0.90 ± 0.05 Gy neutron, while the patient in the CARL event had 2.6 Gy gamma dose from event reconstruction. Since the average gamma energies are almost identical in these two cohorts, it is possible to estimate the deterministic neutron relative biological effectiveness (RBE_d) for PPHA formation in a criticality event. The neutron RBE_d calculated in this way is an average value over the neutron fission energy spectrum and is found to be 3.4 ± 0.6, in good agreement with the currently recommended value of 3 for acute neutron dose to red marrow.**
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Key words: accident analysis; biological indicators; dosimetry; relative biological effectiveness

INTRODUCTION

USING ARCHIVAL peripheral blood slides from radiation accident patients, we have recently described the pseudo-Pelger Huët anomaly (PPHA) in neutrophils as a new radiation-induced biomarker in humans, useful for dosimetry not only immediately after a radiation incident but also potentially helpful as a tool in retrospective dosimetry (Goans et al. 2015, 2017, 2019). Also PPHA has been described recently in animal species exposed to chronic radiation exposure (Hayes et al. 2021). The PPHA morphology in neutrophils appears to be induced within 12 h post-exposure and has been seen in several cases to be persistent up to 16 y, reflecting a stable radiation-induced mutation.

The Pelger-Huët anomaly was initially described by Karl Pelger (Pelger 1928) and later defined by G.J. Huët (Huët 1931) as a mutation with autosomal dominant inheritance. PPHA is generally used to denote the acquired syndrome from an exogeneous agent as opposed to the autosomal dominant type. In this case, PPHA results from radiation damage to red bone marrow, and the cells are characterized morphologically by round, oval, bean-shaped, or symmetric bilobed nuclei joined by a thin mitotic bridge. PPHA affects all granulocytes but is most evident in neutrophils. The anomaly is caused by a decreased amount of the Lamin B receptor (LBR). The B-type lamins are the building blocks of the cell's nuclear lamina, and LBR expression increases during normal human granulocyte maturation. The LBR gene is now known to be located on the long arm of chromosome 1, 1q42.12 (Colella and Hollensead 2012).

In conjunction with the Radiation Accident Registry at the Radiation Emergency Assistance Center/ Training Site (REAC/TS), the frequency of PPHA cells from selected patients in the 1958 Y-12 criticality accident has been compared to that from the patient in the 1971 ^{60}Co accident at the USAEC Comparative Animal Research Laboratory (CARL) (both accidents occurred in Oak Ridge, TN). Since the average gamma energies are almost identical in these two cohorts, it is possible to estimate the deterministic neutron relative biological effectiveness (RBE_d) for PPHA formation from a criticality spectrum.

EXPERIMENTAL METHOD AND RESULTS

We have examined a complete set of archival peripheral blood smears from eight patients involved in the 16 June 1958 Y-12 criticality accident (patients A–H; average age 39.9 ± 9.9 y; RBE weighted dose 0.29–4.61 Gy-Eq). In

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addition, we had available peripheral blood slides from a single male patient (age 33 y) involved in the 1971 Variable Dose Rate Irradiation Facility (VDRIF) ^{60}Co accident (4 February 1971; 63 TBq source; 2.6 Gy skin dose, 1.44 Gy midline dose). VDRIF was located at the Comparative Animal Research Laboratory (CARL) in Oak Ridge. The retrospective dosimetry for each of these accidents has been published elsewhere (Hurst and Ritchie 1959; Beck 1980; Mclaughlin et al. 2000).

Fig. 1 shows typical bilobed PPHA cells from patient A in the Y-12 accident (L) and from the patient in the CARL accident (R). In conjunction with the Radiation Accident Registry at REAC/TS, the frequency of PPHA cells has been compared from selected patients in the 1958 Y-12 criticality accident and from the patient in the 1971 ^{60}Co accident at the USAEC Comparative Animal Research Laboratory (CARL). These frequencies are summarized in Table 1. All slides were collected by the same procedure, Wright-Giemsa stained at the time of the accident, and stored in identical dry storage. An unblinded analysis of the archival slides was performed by the first author. For each slide, at least 500 neutrophils were evaluated for the PPHA anomaly, and percentages were calculated.

Patients A, C, and D in the Y-12 accident are selected for analysis here. They are described as having an average dose of 2.53 ± 0.14 Gy gamma + 0.90 ± 0.05 Gy neutron, while the patient in the CARL event had 2.6 Gy gamma dose from event reconstruction. The gamma energies are approximately the same in these two accidents (1.25 MeV average for the two ^{60}Co gammas and ~ 1 MeV for the average gamma energy from the criticality spectrum). Furthermore, demographics are similar between the two accidents (all male; CARL subject 33 y, Y-12 average 43 ± 7 y). In addition, 39 zero-dose subjects are included for comparison in Table 1.

Fig. 2 shows that there is approximately a linear increase in PH cell frequency with absorbed dose for patients in the Y-12 accident. With this in mind, we have

$$f_\gamma = kD_\gamma \quad (1)$$

$$f_{\gamma+n} = k\ D_\gamma + RBE_d{}^{*}D_n\ , \quad (2)$$

where f_γ and $f_{\gamma+n}$ are the frequencies for PH cell formation in the gamma and criticality accidents, respectively; k is the slope of the linear relation; D is the gamma or neutron dose; and RBE_d is the deterministic relative biological effectiveness for PH formation averaged over the neutron criticality spectrum. From eqns (1) and (2), we can solve for RBE_d:

$$RBE_d = \frac{D_\gamma}{D_n}\left(\frac{f_{\gamma+n}}{f_\gamma} - 1\right) \quad (3)$$

From these data, it is possible to estimate the spectrum-averaged neutron RBE for PPHA formation. The deterministic neutron RBE_d calculated in this way is 3.4 ± 0.6, in good agreement with the currently recommended value of 3 for acute neutron dose to red marrow (IAEA 2005).

Analysis of the PPHA percentage in all cases was performed by the first author. The mean and the standard error of the mean (SEM) for each case are presented herein. The SEM was calculated using a binomial approximation to the Gaussian distribution since the observed quantities are percentages. Historically, individual repeatability from a given scorer on peripheral blood slides was <0.5%. In addition, the Cohen kappa statistic has been calculated to assess inter-observer variability. Cohen's kappa statistic (Cohen 1960), κ, is a statistical measure of inter-rater agreement for categorical items. It is generally thought to be a more robust measure than a simple percent agreement calculation, since κ takes into account the agreement occurring by chance. In these studies, κ was calculated to be 0.87, reflecting generally good agreement between REAC/TS observers.

DISCUSSION

The Radiation Emergency Assistance Center/Training Site (REAC/TS) was begun in 1976 and operates as a U.S. Department of Energy (US DOE) asset for the medical management of radiation accidents with consultation both in the United States and internationally. The Radiation Accident

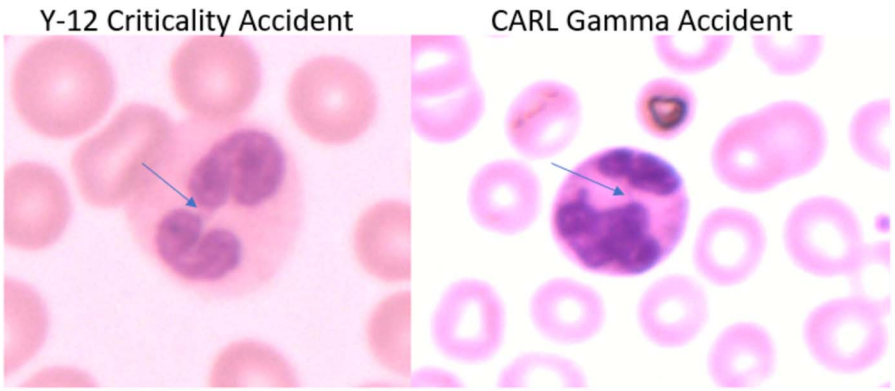

Fig. 1. Typical pseudo-Pelger Huët cells: Y-12 patient A (L) and CARL patient (R).

Table 1. Frequency of PPHA cells.

Subject	Gamma Dose (Gy)	Neutron Dose (Gy)
Average of Y-12 patients A, C, D	2.53 ± 0.1	0.9 ± 0.05
CARL patient	2.6	
Neutrophil PPHA % (d 1 post-event)		
Y-12 subject A	11.9 ± 0.1	
Y-12 subject C	10.5 ± 0.1	
Y-12 subject D	14.4 ± 0.2	
Average for Y-12 group	12.3 ± 0.3	
CARL subject	8.3 ± 0.1	
Zero dose controls (n = 39 subjects)	5.0 ± 0.5	

Registry is part of REAC/TS and currently houses documentation on >2,700 events, the first event dating to 1945.

Three recent papers have described the pseudo-Pelger Huët anomaly (PPHA) in neutrophils (Goans et al. 2015, 2017, 2019) as a new radiation-induced biomarker, useful for dosimetry immediately after a radiation incident and also helpful as a tool in retrospective dosimetry. Using data from the registry, the frequency of PPHA cells has been compared from selected patients in the 1958 Y-12 criticality accident and from the patient in the 1971 ^{60}Co accident at the USAEC Comparative Animal Research Laboratory (CARL). The purpose of this analysis was to estimate the spectrum-averaged deterministic neutron relative biological effectiveness, RBE_d, for PPHA formation.

In the 1958 Y-12 accident, a leak in a tank containing a uranyl nitrate solution (93% ^{235}U) was discovered but not properly logged. The following day, other tanks were being drained into a 55-gallon drum, and the uranium solution from the leaking tank also entered the drum. The operator nearest the drum noticed yellow-brown fumes rising from the drum's contents and retreated before seeing the Cherenkov blue flash as the criticality excursion occurred. Excursion power output rose for at least 3 min, then ended after 20 min. Patients A, C, and D in the Y-12 accident are described as having an average skin dose of 2.53 ± 0.14 Gy gamma + 0.90 ± 0.05 Gy neutron. A description of the dose reconstruction has been published elsewhere (Hurst and Ritchie 1959).

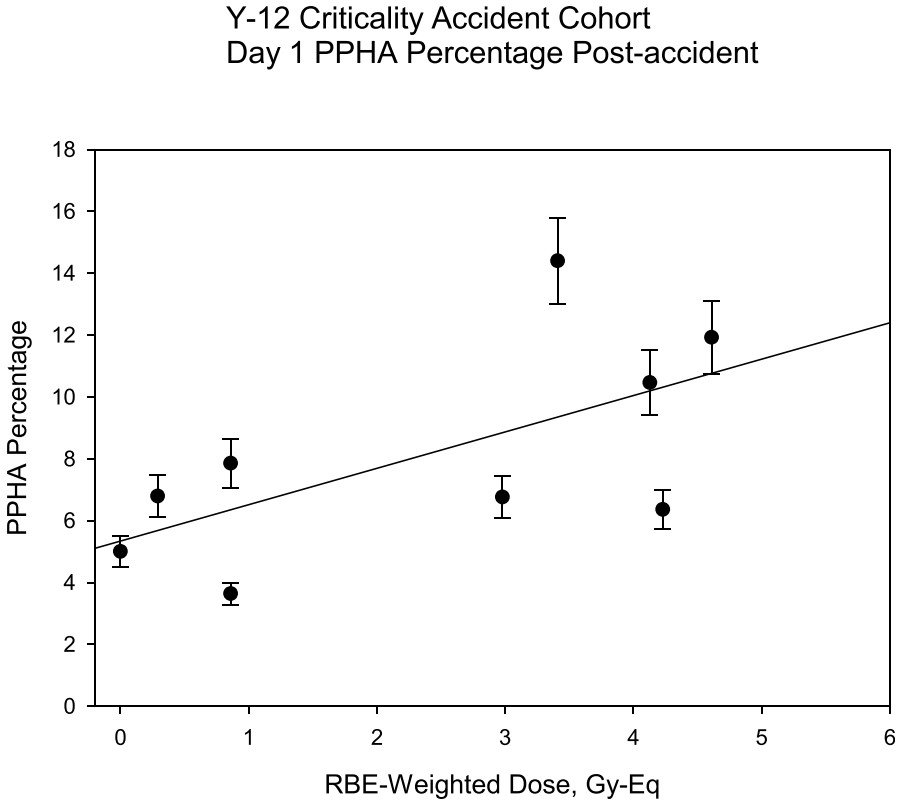

Fig. 2. Plot of PPHA percentage versus RBE-weighted dose (Gy-Eq) for the Y-12 cohort using the RBE of 2 used in the 1958 dose reconstruction.

In the 1971 CARL accident, a technician at a seed irradiation facility walked within 0.6 m of a 63 TBq ^{60}Co source, unaware that the source was unshielded. The patient in this event had 2.6 Gy gamma skin dose from dose reconstruction and from a dosimeter worn at the belt. The dosimetry for this accident has also been published (Beck 1980).

In general, RBE is defined as a factor used to compare the biological effectiveness of different types of ionizing radiation. It is the inverse ratio of the amount of absorbed radiation required to produce a given effect to a standard or reference radiation required to produce the same biological effect (Hall and Giaccia 2017). It is also well known that RBE is a function of linear energy transfer (LET). The Y-12 accident is a ^{235}U liquid criticality event, and the average prompt fission gamma ray energy expected here is 0.97 ± 0.02 MeV (Valentine 1999 and references therein). In the CARL ^{60}Co accident, the two cobalt gamma rays (1.17 and 1.33 MeV) have an average of 1.25 MeV, close to the average gamma energy in the criticality spectrum. Therefore, the gamma components of the two accidents have approximately the same LET.

The average prompt neutron energy of a ^{235}U fission spectrum is approximately 2 MeV (Chadwick and Capote 2023), although it is expected that there would be some spectral moderation here due to water in the containers. From these considerations, it is possible to estimate the deterministic neutron relative biological effectiveness, RBE_d, for PPHA formation from a liquid criticality event. The spectrum-averaged RBE_d calculated in this way (PPHA formation from 2 MeV neutrons relative to 1 MeV gammas) is found to be 3.4 ± 0.6, in good agreement with the currently recommended value of 3 for acute neutron dose to red marrow (IAEA 2005).

CONCLUSION

Using archival peripheral blood slides from radiation accident patients, we have recently described the pseudo-Pelger Huët anomaly (PPHA) in neutrophils as a new radiation-induced biomarker. In conjunction with the Radiation Accident Registry at the Radiation Emergency Assistance Center/ Training Site (REAC/TS), the frequency of PPHA cells has been compared from selected patients in the Y-12 criticality accident and from the patient in the 1971 ^{60}Co accident at the USAEC Comparative Animal Research Laboratory (CARL). Since the average gamma LET values are almost identical in these two cohorts, it is possible to estimate the deterministic neutron relative biological effectiveness (RBE_d) for PPHA formation in a criticality event. The spectrum-averaged neutron RBE_d calculated in this way is found to be 3.4 ± 0.6, in good agreement with the currently recommended value of 3 for acute neutron dose to red marrow.

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