Henri Jammet Memorial Lecture: The Role of Dosimetry In Radiation Accident Response

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I am extremely honored to have been invited to present the first lecture in memory of Dr. Henri Jammet. I first had the opportunity to work with Dr. Jammet during a radiation accident management training course held in Brazil in 1981. I realized immediately the breadth and depth of knowledge he possessed about the topic of radiation accident management and the enthusiasm he brought to any discussion. Henri rarely took personal credit for his many accomplishments, rather giving credit to colleagues and national/international programs he represented and defended with vigor and enthusiasm.

One cannot reflect on the role of dosimetry in radiation accident management without briefly revisiting the pioneering work of Jammet and colleagues following the Vinca accident, affecting six (6) physicists, that occurred on October 15, 1958. Initial dosimetry utilized measurements of neutron induced radioactivity in body sodium as well as personal objects carried by respective individuals Gamma doses were estimated by physical dosimeters in place prior to the accident as well as with time-motion studies and personal interviews of the affected individuals. These dosimetric data collected over the first 10 days post-exposure were later confirmed (by October 30) by observed hematological disorders. As you recall, the sophisticated techniques using induced lymphocyte dicentrics and other biomarkers were not yet available Individual patient care was therefore based on the clinical course, including early prodromal signs and symptoms, hematological findings, skin reactions, visceral/genital changes, and biochemical findings. Dr. Jammet wrote in a review of patient treatment, "In view of the lack of precise information concerning the doses of radiation received, we had to fall back on classical symptomatic treatment as dictated by the clinical developments avoiding, as far as possible, any action likely to interfere with subsequent measures. Faced with a desperate situation, tending toward a fatal outcome, we decided to attempt hitherto untried methods of treatment based on the most recent experimental findings," (Jammet, 1960). Unfortunately, many additional serious radiation accidents have occurred since Vinca. What have we learned from these experiences and has the evolution of modern dosimetric techniques improved medical management? In this regard, we need to explore the techniques of internal dosimetry, as well as radiation cytogenetics

Internal Dosimetry Aspects of Radiation Accidents

There are 68 radiation accidents in the files of REAC/TS that involve internal exposure, that is, instances in which radioactive material became incorporated into the body of one or more patients through inhalation, ingestion, contaminated wounds, or (rarely) direct absorption through intact skin. Thirty of these accidents involved medical misadministrations, of which one resulted in a fatality. Several other misadministrations involved the correct radiopharmaceutical dosage and the correct patient, but an unknown pregnancy at the time of administration resulted in a high absorbed dose to the fetus, or the patient continued to nurse a breast-feeding infant after the administration, resulting in a high absorbed dose to the child. Although a few cases involved administration of a radiopharmaceutical to the wrong patient, the vast majority of incidents involved over-dosages due to one of two errors: 1) a numerical error in radiopharmaceutical dosage preparation, e.g., preparation and administration of 3.7 GBq (100 mCi) when 3 7 MBq (100μCi) was intended, or 2) a procedural error, in which an amount of radiopharmaceutical appropriate for a different procedure was administered The most common accident of this type involves I-131, and in almost every case, human error was the direct cause of the accident.

The other internal exposure accidents in the REAC/TS Registry all involve the uncontrolled dispersion of radioactive materials, whether by human error, as in the case of the Goiania Cs-137 accident (Maletskos 1991), or by equipment malfunction, as in the Hanford Am-241 accident (Thompson, 1983). Of these accidents, the majority (25 of 38) involved the failure of a glovebox or other containment enclosure used for working with radioactive materials. Six relate to reactor operations or weapons testing, and the remainder involved industrial operations relating to ruptured radiography sources or uranium hexafluoride exposure in fuel cycle facilities. One case was an attempted suicide, in which a person drank a solution of radium bromide The attempt proved successful five years later, when the subject died of a radium-induced osteosarcoma (Guskova and Baysogolov 1971).

The details of the major radiation accidents that have involved internal exposure, such as the Goiania and Hanford accidents are well known, and will not be repeated here Rather, we will discuss the impact of internal exposure on radiation accident response.

The primary difference between radiation accidents that involve internal exposure and those that involve only external exposure is that the former will always result in protracted exposure and absorbed dose External exposure may also be protracted if radioactive material has been misappropriated or dispersed, such as in the Juarez Co-60 accident, but once the event is discovered and the radioactive material is removed, exposure ceases. The duration of an internal exposure is determined by the physical and biological half-lives of the incorporated radioactive material, and is frequently unaffected by response measures

However, in some special cases, decorporation therapy, diuretics, or simply increasing fluid intake may be used to increase the excretion rate of incorporated radioactive materials, adding another aspect to patient care. Prussian Blue was used successfully in treating victims of the Goiania accident, but diuretics were mostly ineffective (Farina et al. 1991). Hydration therapy is commonly used to increase the turnover rate of body water and has been successfully applied to intakes of tritium (Guskova and Baysogolov 1971).

Other considerations in handling internally contaminated radiation accident victims also relate to bioassay measurements In general, the activity levels in the whole body or in excreta samples may be several orders of magnitude greater than usually encountered in occupational radiation protection operations Consequently, normal radioanalytical procedures may have to be modified to avoid dead time or detector saturation problems. For example, in whole body counting victims of the Goiania Cs-137 accident, the standard reclining chair geometry, in which the patient's torso is approximately 30 cm from the detector, could not be used because of the extremely high counting rates observed. Instead, a distant geometry was developed, in which the patient was seated some 2 meters from the detector (Oliveira et al 1991).

In these cases of internal contamination, standard techniques of in-vivo and in-vitro measurements are employed These techniques vary in time requirements, especially for excreta analysis and are often complicated by a varying mathematical models used to determine body burdens of specific radioisotopes. Consideration must also be given for chemical/physical forms of contaminants, and medical intervention which alters translocation, deposition, and excretion rates upon which many models are based.

Mass casualty situations call for extraordinary means for both conventional medical and radiological triage. Experience has demonstrated that internal contamination is usually more difficult to assess under triage conditions; therefore, in mass casualty accidents, simple screening may be the most practical approach in early triage. This technique was employed quite successfully by the Brazilians following discovery of the cesium-137 accident in Goiania where 129 persons were found to be internally contaminated (IAEA, 1988). In cases of several hundreds to thousands of internally contaminated individuals, primary screening using simple survey meters is advisable. Persons can then be triaged into three groups based on predetermined levels of estimated internal contamination. One approach is to relate contamination levels to corresponding levels of committed affected dose. Using this approach triage groups can consist of 1) those persons not of particular concern, 2) those with estimated levels requiring more thorough evaluation; and 3) lastly those persons with high levels requiring prompt, accurate assessment, and appropriate medical treatment. Regardless, it may be days to weeks before a more complete assessment of internal contamination is completed. A useful reference in this regard is a IAEA.TECDOC-746.

Biodosimetry: Radiation Cytogenetics

Soon after the discovery of radiation, investigators observed in the 1930s that ionizing radiation induces genetic mutations and chromosomal aberrations in both irradiation plant and mammalian cells. The impressive body of data obtained in the early studies established, not only the types, patterns, and kenetics of aberration breaks and rearrangements, but the concepts and principles that apply directly to human cytogenetic data today Human cytogenetics was not possible until methods were found in the late 1950s for obtaining preparations of human lymphocyte chromosomes. The most important discovery was that of phytohemagglutinin, a bean extract commonly used as an anticoagulant. Phytohemagglutinin was found to stimulate peripheral blood lymphocytes to divide in culture. Subsequently the use of colcemid, a chemical that prevented the formation of spindle fibers at division, plus improved harvest techniques, provided well spread metaphases with chromosomes that were morphologically superior. These new methods provided for the beginning of human cytogenetics and more specifically radiation cytogenetics Initial studies on the effects of radiation in human cells demonstrated that dose dependent aberrations induced in-vivo were both qualitatively and structurally the same as observed in cell in-vitro This finding was the basis for using cytogenetic aberrations induced by radiation as a measure of human exposure. Though easily identifiable, a asymetrical exchange aberrations were the primary determinant of dose for recent exposure, not until the 1970s when further developments in differential staining methods and standardization of procedures did data obtain from metaphases in first division provide results that were consistent between laboratories. Other developments in staining methods (i e., Giemsa banding and more recent fluorescent DNA probes) allowed analysis of uniquely specific banding patterns of individual chromosomes. The new procedures enabled investigators to see more of the persistent translocations, thus enhancing the capabilities in retrospective dosimetry studies Later, new techniques for micronuclei assays were established that allowed for more precise dose response coefficients and greater utility as a biodosimeter; however, both micronuclei and translocations fall short in the assessment of exposure on an individual bases at dose levels less than 30 to 50 cGy The shortcomings of these endpoints are primarily due to the relatively high background frequencies and considerable inter- and intra-individual variation associated with background levels, age, sex, and radiosensitivity Using standard techniques, dicentrics currently represent the best biological indicator of dose in cases of recent external exposures to doses of >10 cGy Furthermore, stable rearrangements have been shown to amply provide retrospective dosimetry for population cohorts exposed to doses of >5 cGy. All cytogenetic endpoints based on the random induction of aberrations can provide considerable qualitative information on the nature of both internal and external accidental exposures (i e., level of homogeneity, radiation quality, relative degree of protraction and severity). The experience of major cytogenetic dosimetry centers since 1975 has shown from studies of hundreds of suspected cases of overexposures that biodosimetry studies are particularly important in providing, in more cases than not, evidence that exposure to a significant dose of radiation was highly unlikely (Excellent reviews on this topic can be found in Bender, 1988 and Tucker, 1997)

Since the 1950s, it has become firmly established that the use of radiation cytogenetics is one of the valuable tools for assessing dose and thereby providing another tool for determining both prognosis and treatment course. Hundreds of dosimetric estimates have been carried out in serious radiation accidents in which in any given situation, fewer than six persons were involved (Littlefield, 1991). A question more frequently asked however is related to the value of cytogenetic dosimetry in serious radiation accidents involving multiple casualties.

The application of cytogenetic dosimetry following medically significant doses in multiple casualties has been limited. However, two well known cases, namely the Chernobyl Nuclear Power Plant accident in 1986 and the Goiania cesium-137 accident in 1987 are excellent examples. We are all aware of the remarkable efforts both in the Former Soviet Union and Brazil on the part of cytogenetic specialists to complete large numbers of dose estimates in short time periods The results of these dosimetry estimates are well documented in numerous publications and do not require additional discussion in this presentation. There are however, additional cases that can be used to demonstrate the usefulness of cytogenetic dosimetry in large populations potentially exposed to medically significant doses.

In February 1996, two cobalt-60 radiography units were stolen in a large US city and after various parts were removed, the units were sold for scrap metal The units contained activities of 333 GBq (9 Ci) and 1.6 TBq (43 Ci) respectively. The 1 6 TBq source became dislodged from the camera and went unnoticed for several days. Twenty-two (22) individuals were identified at risk to overexposure. These individuals ranged in age from 2-60 years old Although no individual demonstrated early signs or symptoms of acute radiation injury (the doses were protracted over one week), REAC/TS was contacted to conduct cytogenetic dose estimates on each person. Radiological monitoring of the scrap metal facility revealed exposure levels from 2 cGy per hour, a few meters from the source, to an excess of 500 cGy per hour 0 3 meters from the source.

Subsequently, each individual was seen by a physician and blood samples were drawn for cytogenetic dosimetry. The results are shown in Table 1 and demonstrate that no individual received a medically significant dose. This information was extremely useful for purposes of counseling the individuals.

Another case demonstrates the use of cytogenetics when the exposures are known or suspect but individuals are free of symptoms of acute radiation injury. In November 1992, a 140 GBq (3.8 Ci) brachytherapy source was inadvertently left in a patient's tumor when proper procedures were not followed in a radiotherapy clinic The patient subsequently died 4 ½ days later. Over 90 persons were potentially overexposed, some of whom handled the source when it became dislodged from the patient's tumor. The US Nuclear Regulatory Commission conduced time/motion studies based on interviews with individuals who were involved Based on these time/motion studies, 33 persons were identified for additional studies using cytogenetic dosimetry. Four cytogenetic research associates with REAC/TS were responsible for initiating and harvesting cultures over a two-day period. Subsequently, they spent full-time scoring slides from these cultures Over a seven-day period, 500 metaphases were scored for each at risk

individual Dose estimates for the nine persons identified at greatest risk ranged from 0-16 cGy. These results are shown in Table 2 (US NRC, NUREG, 1480). Several individuals were suspected of having high dose to extremities due to close proximity or actual handling of the iridium-192 source Extremity dose estimates range from 10 cGy to a high of 160 cGy.

These two cases demonstrate the use of cytogenetics when potential exposures are in question involving multiple individuals. More and more cases of this nature are being reported in the US In these cases, and in many others, the value of cytogenetics is often to demonstrate that medically significant exposures have not occurred. Results of cytogenetics in these cases often end up in litigation procedures and are useful in demonstrating little or no dose.

Whether one is dealing with a case of one exposed individual or multi-casualties, cytogenetic findings will differ based on exposure scenario There are five scenarios worthy of mention: 1) uniform total body exposure to radiation of a single quality, rapidly delivered. This could be referred to as the best case dosimetry scenario; 2) non-uniform exposures to penetrating low LET radiation. This prompts the questions, which lymphocytes were where?; 3) internally deposited radionuclides and the associated non-uniform doses. This presents and issue of "bullets and targets," particularly associated with radionuclides that emit high LET alpha particles or poorly penetrating gamma or beta radiation; 4) chronic and/or protracted exposures to low LET radiation This presents the dilemma of radiological versus clinically relevant dose; and 5) acute/fractionated/chronic/ whole/partial body exposures to mixed quantities of radiation from external source and internal emitters This could be referred to as the worst case dosimetry scenario (Table 3). These scenarios are discussed in more detail in a publication by Littlefield (Littlefield, 1990). These scenarios and the problems presented for the cytogeneticist could obviously compound the issue of using cytogenetics in mass casualty situations. Considering the time required for generating dose estimates following mass casualty accidents and the problem of where, when, how long, shielding, etc., present additional complications All of this leads to a philosophy of initial cytogenetic screening among selected populations followed by more definitive tests at a later time.

The response community has not yet been tested in situations where several hundreds to thousands of persons may require immediate biodosimetry studies. The scenarios for such situations could involve nuclear weapons detonation or the use of radiation dispersal devices following terrorist activities. These events would obviously be complicated by concurrent conventional trauma. One must assume there exists a balance between the practicality for biodosimetry for large populations and the overall medical capabilities following mass casualty nuclear accidents If such an event occurs, laboratories worldwide may be called upon, including the REMPAN network, to assist in all response aspects, including biodosimetry. The developing techniques for cryopreservation of lymphocytes and their transport in large sample numbers to appropriate laboratories may facilitate the response capabilities. Although, currently the technique is more applicable to epidemiological studies.

The future of biodosimetry almost certainly relies upon further developments forthcoming in the area of molecular cytogenetics and the technology of digitally enhanced computerized imaging Since the early

applications of molecular techniques in cytogenetics (Meyne, 1986), much progress has been made in building of large libraries of chromosome specific DNA probes used to study mutagen induced chromosomal aberrations. As new techniques and applications are developed, greater resolution of DNA damage and understanding of the formation of chromosome aberrations will be possible and the application of cytogenetic biodosimetry will assuredly expand to provide greater capability in studies of low-dose exposures and insite into the complex interactions induced by high doses. In addition to developments in the biology in the induced DNA damage, new techniques in computer technologies will make quantitatively larger assays economically feasible, allowing for narrower confidence intervals on dose estimates for exposed populations and on an individual bases The use of pre-employment (pre-exposure) assays to establish data bases of individual background frequencies of aberrations and micronuclei may be feasible in the near future.

What would Dr. Jammet have shared with us at this point? I have no doubt that he could have given us a better review and more complete vision for the future, nevertheless, as he mentioned to me on many occasions, the physician will always treat the patient and not the dose. When Dr. Jammet and I would discuss things other than radiation accident management, he would usually talk of flowers and his favorite dessert. If he were with us here today, I'm sure he would advise that we should always take our roles in radiation accident management seriously but never forget to stop, smell the roses, and eat plenty of strawberries.

Table 1: Results of Cytogenetic Dosimetry (REAC/TS Registry Case #1673)*

PATIENT	AGE	# CELLS	# DICENTRIC	DOSE ESTIMATES (CGY)
CS	3	500	1	<10
CS	2	500	1	<10
JS	24	500	1	<10
JS	26	500	0	<10
CA	40	500	0	<10
JA	29	500	1	<10
MM	22	500	0	<10
TW	29	500	1	<10
BC	45	500	1	<10

*13 others with age range from 18-60 had dose estimates reported as background based on zero dicentrics found in 200-300 cells studies.

Table 2: Comparison of Calculated Whole Body Doses with Cytogenetic Evaluations

Individual	Metaphases scored	No. dicentrics observed	Dose estimate *		90% Confidence interval
			Based on time-motion studies (cGy)	Based on cytogenetic evaluation (cGy)	(cGy)
SHM Dietician	500	1	0.6-0.4	0	<1-12
SHM Resident B	500	2	13-4	~6	<1-20
SHM Resident C	500	3	20-6	~10	3-25
SHM Resident M	500	3	9-6	~10	3-25
SHM CNA C	500	4	22-16	~16	6-29
SHM CNA E	500	2	15-10	~6	<3-20
SHM LPN B	500	3	17-11	~10	3-25
SHM Maintenance	500	2	4-2	~6	<1-20
Man A	500	1			
Friend A	500		9-2	0	<1-12

* Estimate of "equivalent" dose to whole body for iridium-192 gamma rays. For purposes of this report, 1 cGy = 1 cSv

(NUREG 1480, 1993)

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