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August 31, 1983

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REPORT OF FOREIGN TRAVEL BY **L. GAYLE LITTLEFIELD, ORAU**

Attached is a copy of the report prepared by L. Gayle Littlefield covering her travel to the Netherlands and Austria during the period July 1-12, 1983. Dr. Littlefield participated in and presented an abstract at the 7th International Congress of Radiation Research and represented REAC/TS at an IAEA Technical Committee Meeting on "Medical Planning of Overexposed Persons."

The report has been reviewed and does not contain any classified information.

W. D. Adams

W. D. Adams, Acting Director
Energy Programs and Support Division

ER-111:MW

Attachment:
Trip Report

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FOREIGN TRAVEL REPORT

July 1, - July 12, 1983

L. Gayle Littlefield, Ph.D.

Medical and Health Sciences Division
Oak Ridge Associated Universities
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August 19, 1983

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A. Summary

This trip report is being submitted by L. Gayle Littlefield, Ph.D., Director of the Cytogenetics Laboratory of the Medical and Health Sciences Division of Oak Ridge Associated Universities (under Contract #DE-AC05-75OR00033 with the U. S. Department of Energy). The official portion of this trip extended from July 1, 1983 through July 12, 1983.

The destinations of this trip were Amsterdam, The Netherlands, where the 7th International Congress of Radiation Research was held from July 3-8, 1983, and Vienna, Austria, for the traveler to attend the International Atomic Energy Agency Technical Committee Meeting on "Medical Handling of Overexposed Persons" held from July 11-15, 1983. On July 11 and 12, 1983, the traveler attended the latter meeting at the invitation of Dr. A. Bianco, Scientific Secretary, IAEA.

The purpose of this travel assignment was twofold: the first, to participate in and present an abstract entitled "Six year cytogenetic follow-up of an individual heavily contaminated with Americium 241" at the 7th International Congress of Radiation Research. Secondly, Dr. Littlefield represented REAC/TS as an invited member of a technical committee convened by The International Atomic Energy Agency in Vienna. The purpose of the committee meeting was to discuss the subject material to be included in future IAEA publications on the medical criteria for treatment of overexposed persons.

The full report represents a summary of the contents, the highlights, and the traveler's impression of both meetings.

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Actual costs of the travel are itemized as follows:

Transportation:	$ 1272.13
Lodging:	563.30
Per diem:	303.50
Registration fee:	$ 205.00
TOTAL:	$ 2043.93

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B. Comprehensive and Detailed Trip Report

7th International Congress of Radiation Biology

The 7th International Congress of Radiation Biology was held in Amsterdam, The Netherlands, July 3-8, 1983. The meeting was attended by 1304 registered participants from 45 different countries. The largest contingent of scientists (over 400 total) was from the United States, and included a number of participants from various DOE facilities (i.e. Brookhaven, Argonne, Hanford, Lawrence Livermore, Los Alamos, and Oak Ridge National Laboratories, and ORAU).

Site of Congress:

The Congress was held at the RAI (pronounced Rī) on the Southern outskirts of the city of Amsterdam. The RAI, which we learned during the closing ceremony was the Dutch abbreviation for Bicycle and Automotive Institute, is a sprawling, very modern International Congress Center, complete with a number of large well-equipped auditoriums (Grote), several smaller lecture rooms, a bank, post office, restaurants, and bars. The facility was quite impressive, and certainly large enough to contain a meeting of our size. The only disadvantage that I found with the Congress Center was the distance between the seven various meeting halls where posters were displayed. The RAI was conveniently located with regard to lodging accommodations for participants. Several modern, high-rise hotels were within a 15 minute walking distance, and a combination tram-railway station with multiple interconnections to all parts of the city was located within 10 minutes walking distance from the meeting facility.

Planning and Organization of The Congress:

The Congress was well-organized and compliments are due members of the Organizing Committee (especially J. J. Broerse, Secretary General) and to the Scientific Program Committee. General announcements for the meeting appeared over a year in advance, and the first call for papers in February 1983. Correspondence regarding scientific presentations was handled promptly, and Program outlines and formats for presentations were mailed to prospective participants several weeks in advance. Likewise, the Dutch Travel Agency, Wagon Lits, was very accommodating in reserving lodging, as was Matisse Travel in scheduling overseas air travel at reduced rates for members of the U. S. Radiation Research Society.

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Registration and Information Desks were open on Sunday, July 3 from 12.00 - 18.00 hours, and check-in of participants was accomplished without delay. Upon registering we received Congress badges, a Revised Program Outline, and five volumes of the published abstracts of the proffered papers. Throughout the remainder of the week, Registration, Information, and other Service Desks remained open in the lobby of the main hall of the Congress Center, and were staffed by helpful and congenial persons.

The Committee for accompanying persons and social activities also did a commendable job in arranging a special program on Monday evening by the National Youth Orchestra which was presented at the Concertgebouw, and a Congress excursion on Wednesday afternoon to the town of Hoorn. Participants also received a week tram-pass for travel on all public transportation systems and a ticket for a canal trip through the historic district of the city.

Scientific Program:

The Scientific Program Committee for the Congress consisted of 29 persons and was chaired by G. W. Barendsen. The Organizing Committee designed a scientific program with a structure different from that used in earlier Congresses. As noted by the Committee, the specific aims of the revised format were to optimize the information exchange and interaction among participants. The number of parallel sessions was reduced in an effort to avoid overlap of subjects of interest to the same participant. To accomplish this, the vast majority of contributions were presented and discussed in 33 poster-workshop sessions. Each of these sessions was introduced by an invited speaker, and summarized by an invited rapporteur. Either six or seven poster-workshops were presented concurrently on each day of the Congress.

The Scientific Program of this Congress was divided into five broad groups, including: A. Chemistry and Physics; B. Biology; C. Somatic and Genetic Effects; D. Tumor Biology and Therapy; E. Dosimetry, Radionuclides and Technology. Each of these categories included 6-8 specific research areas, for example, the Scientific Sessions in B. Biology included:

B. 1 Radiation biochemistry-mechanisms of damage

B. 2 DNA damage and repair in cells

B. 3 Effects on DNA and membranes

B. 4 Mutagenesis and chromosome changes

B. 5 Lethal, sublethal and potentially lethal damage in cells

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B. 6 Sensitization and protection

B. 7 Repair in cells, cell contact

Participants submitted two-page "extended abstracts" in February, which were assigned to specific subject areas. Approximately 1000 contributions were presented.

In addition to the proffered papers and invited contributions presented in the poster-workshops, two parallel semi-plenary lectures were presented by invited speakers in the two large auditoriums on Monday, Tuesday, Thursday and Friday morning.

Although the topics of primary interest to me were those studies related to human or mammalian cytogenetics, a number of other study areas were of peripheral interest to our work at ORAU, or directly relevant to the task of NCRP Committee 40 in defining biological effects of radiations of differing LET. For this reason I attended a variety of presentations which are abstracted in the following section.

Highlights of selected contributions that related to ongoing work at ORAU

For the last several years our research efforts have focused on 1) using cytogenetic methodology to assess the induction or long-term persistence of aberrations in lymphocytes of persons having recent or previous exposures to ionizing radiation 2) applying cytogenetic techniques in quantifying the cellular effects of radiations having differing LETs 3) assessing the risk of induction by chemicals of transmissible cytogenetic lesions in female germ cells and 4) in defining parameters that affect the expression of cytogenetic hypersensitivity in persons and animals at increased risk for malignancy. Posters, semi-plenary lectures, and introductory talks that addressed these various subjects were presented on several different days in a variety of different sessions, and for simplicity in highlighting important findings, I have grouped papers by subject areas (which do not necessarily reflect the subject areas to which the posters were assigned in the Program). The information presented in each poster was summarized in "extended abstracts" which were limited in length to two single-spaced typed pages. Because tables and figures could be included in the abstracts, this format more closely resembled "brief reports" than the typical 250 word abstract. Since the extended abstracts were published prior to opening day of the Congress, I will not reiterate many technical details presented in the printed text, but will

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note significant findings that I considered most relevant to ongoing work in our laboratory.

Cytogenetic methods in population monitoring and biological dosimetry

A number of papers which dealt with cytogenetic methods in population monitoring were presented in a variety of different sessions. In addition, one poster-workshop session was devoted to biological indicators of dose.

Dr. David Lloyd of the National Protection Board, Harwell, gave the introductory lecture in this session, Dosimetry: Biological Indicators, in which I presented a poster. Although the majority of the participants in this poster-workshop were cytogeneticists, Dr. Lloyd gave a nice overview of the utility of a number of different systems that have been used as biological indicators. He introduced the subject by noting that indicator systems should have the following attributes: 1) The systems should require a biological sample that is obtained from the donor with a minimum of trauma; 2) Measurements of effect must be reproducible, and should not show large variability between different donors, nor in measurements made between different laboratories. 3) The effects that are to be measured must persist for a reasonable period of time, i.e. those effects which are transient will obviously not be of great utility when doses are estimated some time after an exposure. 4) The biological effect to be measured must show good correlation with radiation dose, and it is important that the effect can be measured at relatively low doses (less than 50 rad). He noted three possible biochemical systems that may have potential as indicators of dose, including alterations in excreted metabolites, serum enzymes, or serum thymidine. Each of these systems makes use of body fluids (i.e. either urine or serum) which are easily obtained. One of the primary problems would be how long after exposure altered biochemical parameters persist; that is, whether or not the altered products are transient in nature, or will still be measurable for a reasonable time after an exposure. With reference to this point, he called attention to a poster presented in the session which suggested that alterations in serum thymidine may be observed after exposure of mice to doses of as low as 0.5 gray. The effect has not been induced after in vitro exposures to radiation, however, after in vivo exposure, there is a reduction in the uptake of H_3-thymidine when serum from irradiated mice is added to fibroblasts grown in cell culture. This system may have some potential, but as yet has not been

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tested in other species.

Under possible cellular dosimeters, he listed: membrane effects, mitogen response, reticulocyte count, stem-cell count, germ-cell effects, and chromosome studies. With regard to membrane effects, some interesting new studies have shown alterations in lecithin binding after exposure to some types of radiation. Likewise, studies have suggested that radiation exposure decreases transformation response of lymphocytes. However, the response is quite variable among donors and quite variable at different doses and for this reason cannot be accurately "calibrated". With regard to alterations in reticulocyte count, some recent studies have shown a depression in reticulocyte counts in mice at doses of as low as 13 rad. Similarly, recent studies in dogs have shown decrease in the number of stem cells after exposures to doses as low as 25 rad, and based on studies of germ cells in testicular biopsies, decreases have been seen at doses as low as 10 rad.

To date, the most reliable biological indicator that has been described for the estimation of radiation dose is the use of radiation-induced chromosome lesions in lymphocytes. All that is required to undertake a cytogenetic study is about 5 ml of whole blood, which can be obtained with a minimum of trauma. Both in vivo and in vitro studies have shown that effects are highly reproducible, and that there is little variability among donors. Likewise, although there is some variability in measurement between laboratories, most generate similar results. Because the lymphocyte is a long-lived cell with a half-life of approximately one thousand days, the effects persist for a long period of time and can be evaluated many years after exposure. Induced cytogenetic lesions not only show good correlation with radiation dose, but also some indication of radiation quality may be obtained from cytogenetic studies by assessing the distribution of induced lesions in damaged cells. The effect is measurable to doses in the range of about 10 rad for low-LET radiation, and whole body doses as low as approximately 5 rad may be measured after exposures to high-LET radiations such as fission neutrons. Because cytogenetic effects are studied in a circulating blood cell, cytogenetic dose estimates give indication of equivalent whole body dose and may not accurately represent doses in instances of partial body exposure.

In terms of partial body exposures, Dr. Lloyd discussed recent studies that suggested the possibility of using skin fibroblasts cultured from areas

directly in the radiation field as an indicator of dose to a specific portion of the body. Another approach that is currently under investigation, is the study of epithelial cells surrounding hair follicles for induced cytogenetic damage. There is some promise in studying this type cell since the follicular cells are in a G_0 (resting) state in the follicle, and for this reason, lesions would persist until the first mitosis and not be lost during cellular proliferation. Unfortunately, both the fibroblast and follicular cell systems are quite new and will require a great deal of work to establish their utility in the future.

Several posters dealt with the utility of cytogenetic methods in population monitoring, or addressed in vivo or in vitro variables that affect the acquisition of cytogenetic data in the lymphocyte culture system. Ms. Jan Tawn, of British Nuclear Fuels Limited, summarized ongoing studies of their analysis of radiation-induced chromosome lesions in two-day BrdU-substituted lymphocyte cultures from radiation workers at Windscale. The study population consists of workers with known body burdens of plutonium ranging from 0 - 1480 Bq (acquired by inhalation or puncture wound), and new entry workers with no previous exposures to internal or external radiation. To date, they have observed a marked increase in both stable and unstable aberrations in all three dose groups of plutonium workers relative to those seen in controls, with stable aberrations exceeding unstable lesions in all groups including controls. Simarily, in all groups of plutonium workers the distribution of lesions was overdispersed relative to that expected based on Poisson statistics, as would be expected after exposure of human lymphocytes to high energy alpha particles. Although dicentric frequencies were higher in smokers than in nonsmokers, the increase was not statistically significant. A major point raised by several persons who viewed the poster was that the control subjects are considerably younger (about 20 years) than the population of workers with measurable body burdens of plutonium. Jan indicated that studies are in progress in older control subjects to determine whether age is a confounding variable in their analyses.

Interestingly, the effects of age on aberration induction in human lymphocytes was addressed by G. Stephan and T. P. Chang of the Federal Republic of Germany who presented data obtained after the in vitro exposure of human

whole blood from 25 men and 25 women to 200 rad X-radiation. The age of the subjects ranged from newborn (cord blood) to 85 years. The analysis of proliferation kinetics and aberrations in BrdU-substituted lymphocyte cultures demonstrated that lymphocyte proliferation could not be related to age or sex of the donor, and showed that while there was large individual variability in aberrations (about two-fold differences) the variability was not attributable to the donor's age or sex. We have observed similar wide variability in the frequencies of second division metaphases in early harvest cultures from different persons, and in the frequencies of aberrations induced following the in vitro exposure of blood from different donors to penetrating radiations. Such variability in aberration frequencies can also be pronounced in replicate sets of data scored from cultures from the same persons. These findings emphasize that person to person variability must be taken into account by appropriate statistical methods when defining dose response relationships for lesion induction in lymphocytes.

Regarding in vitro variables that might affect cytogenetic dose estimates, Schmid, Bauchinger and Dresp of the Federal Republic of Germany reiterated a technical point that has been made in several earlier reports, i.e. that accurate estimates of the induction of radiation-induced lesions in lymphocytes can only be made using techniques that allow selection of first division metaphases for quantitation of damage. These authors have shown that after in vitro exposure of lymphocytes to low doses of radiation, the analysis of exclusively first division metaphses (M1) cells (made using FPG methods), yields significantly higher frequencies of radiation-induced dicentrics than conventional techniques. This results from the fact that significant numbers of lymphocyte metaphases may be in their second post-radiation cell division in 48 hr cultures of PHA-stimulated lymphocytes, which results in an artifactual reduction in the frequencies of cells bearing unstable aberrations (due to the mitotic lethality of these lesion classes). To use or not to use BrdU methodology for routine dosimetry estimates was further discussed in the rapporteur's closing remarks. The obvious advantage of the method is that differential staining techniques allow the exclusive selection of first division metaphases for analyses; the disadvantage of the system is that frequently the morphology of the metaphases is inferior on differentiated slides. Suggestions on how to deal with the problem included (1) to initiate

duplicate cultures with and without BrdU, and to use substituted cultures for analysis of proliferation kinetics, and to use unsubstituted cultures for scoring aberrations, (2) initiate all cultures with BrdU, determine percent seconds on differentiated slides, score lesions on cultures stained by routine methods.

In addition to several papers that addressed various factors influencing the assessment of aberrations in lymphocytes from irradiated persons, two posters presented quantitative information on in vitro and in vivo parameters affecting the yield of radiation-induced micronuclei. Bauchinger and Huber described a series of in vitro experiments in which they had observed the following: (1) that the methodology for fixation of cells has significant effects on the number of micronuclei observed (2) that hypotonic treatment with 0.1 MKCl for 8 min at room temperature preserves the morphology of interphase nuclei, and yields more consistent counts, (3) that the distribution of micronuclei was overdispersed in 24 of 30 analyses (4) that different dose response relationships are obtained for 48 hr (linear) and 72 hr (linear-quadratic) data. The authors concluded that there are several problems with the system including their observatins of high background frequencies (220 micronuclei/1000 cells at 48 hr, 140 micronuclei/1000 cells at 96 hr), and their lack of ability to detect effects in cells exposed to less than 30 rad. They further noted that for calibration purposes a standardized culture time yielding a maximum response cannot be recommended. The data presented by these authors show much higher background frequencies of micronuclei than that reported by other groups in earlier studies (i.e. about 5/1000). They attributed these differences to their improved method for hypotonic treatment which allowed them to more accurately count micronuclei in intact cells.

In a second paper on the assessment of micronuclei in human lymphocytes, Norman and his associates from UCLA reported that the background frequency of micronuclei in cultures from control subjects shows a significant positive correlation with subject age. They concluded that studies of radiation workers or other populations exposed to radiation may be misinterpreted if the effects of age and other in vivo variables are not controlled. My personal feelings regarding the use of this method for assessing exposure, is that although scoring may be more rapid, the technique is fraught with many technical

variables that affect precision of "dose" estimates.

The question of potentiation of radiation effects in patients having clinical procedures employing contrast media was also addressed. Several earlier studies have demonstrated significant increases in the frequency of radiation-induced chromosome lesions or micronuclei in lymphocytes of patients after X-ray examination with water-soluble iodized contrast media. The enhanced effect has been attributed to the clastogenic activity of the contrast medium, increased absorption of radiation dose in the presence of the contrast medium, or a combination of the above processes. Based on data obtained in a series of in vitro experiments, Hadnagy and Stephan concluded that the influence of the contrast medium is dependent on the iodine concentration in the blood, and that the only responsible mechanism for the enhanced cytogenetic sensitivity may be the photo-electric effect of the iodine. This could be explained by the higher primary interaction of the photons with iodine leading to an increased number of secondary electrons that transfer their energy to cells adjacent to the contrast medium.

Two reports of follow-up studies on A-Bomb survivors were presented. These were of particular interest because of our ongoing collaborative study with investigators at the Environmental Epidemiology Branch, NCI, and because of the relevance of the A-Bomb biological data in terms of the work of NCRP Committee #40.

Tanaka and his associates presented results of an interesting study in which detailed banding analyses were conducted on early harvest lymphocyte metaphases from selected heavily exposed Hiroshima A-Bomb survivors. Details of their findings have been submitted to the Japanese Journal of Radiation Biology, and Dr. Tanaka agreed to send a preprint of the paper for our use in comparing data we are currently collecting on lesion frequencies in our NCI population study. Of several observations reported in the poster, the most interesting finding was that the distribution of break points involved in symmetrical lesions was not random, but that specific chromosomes and specific chromosome sites were observed more frequently than expected based on chromosome length. Symmetrical rearrangements involving human chromosome 15

were commonly observed whereas rearrangements involving C group chromosomes were noted less frequently than expected. The authors interpreted these observations as suggesting that over a period of several years after exposure, selective processes are operable in the evolution of cells bearing lesions involving specific chromosomes or chromosome sites. We have made similar observations in our analysis of the distribution of persistent symmetrical radiation-induced lesions in both the Y-12 accident survivors, and in the NCI cohort.

In a second poster describing cytogenetic studies in A-Bomb survivors, Honda and his associates presented undated information on the incidence of inherited chromosome lesions in children born after May 1946 to parents who had been exposed during the bombing of Hiroshima and Nagasaki. The study population included 6,628 children having one or both parents exposed within a distance of 2000 meters from the hypocenter of the blasts. When cytogenetic data from 52 hr whole blood cultures from these children was compared with that obtained from a control population in Japan and with reported findings in 59,452 neonates, the authors concluded that there were no significant increases in congenital numerical or structural chromosome aberrations in the cohort of children born to exposed A-Bomb survivors. These authors have previously noted that because the subject children were not examined until they were a minimum of 13 years of age, their data are not useful in estimating the incidence of induced aberrations that carry an increased risk of early neonatal mortality. This issue was also raised in the rapporteur's summary, who pointed out that the incidence of Down's syndrome in the Japanese cohort was 1 in 14,000 cases, whereas approximately 14 cases would have been expected in newborns. This certainly suggests that some selection against severe cytogenetic disorders occurred in these children prior to sampling of the population for radiation effects.

A very interesting paper on the induction of lesions in human lymphocytes after exposure to ionizing radiation during G_2 of the cell cycle was presented by G. Olivieri. Human lympnocytes were exposed in vitro to doses of radiation up to 400 rad, after which tritiated thymidine was added to the culture medium. At varying times after exposure the incidence of radiation-induced lesions was evaluated in metaphases that had not incorporated H_3-thymidine (presumable G_2

cells). The conclusions derived from the study were that in an irradiated G_2 population, the fraction of cells that does not undergo mitotic delay decreases with increasing dose, and that in cells that do undergo mitotic delay, the incidence of aberrations decreases dramatically. This suggests that human G_2 lymphocytes are capable of repairing a substantial amount of radiation-induced damage. Although this paper is not relevant to the use of lymphocytes irradiated during Go for dose assessment, it does provide interesting information on the repair capabilities of lymphocytes irradiated during other stages of the cell cycle.

Variations in cytogenetic parameters in cells exposed to radiations of differing LETs

Posters addressing the cytogenetic effects of radiations having differing LET were also presented in several different sessions. Likewise, an excellent semi-plenary lecture which addressed LET effects was presented by Dr. A. M. Kellerer. The title of his presentation was "Models of Cellular Radiation Action". The format of the presentation was largely descriptive and theoretical, and did not involve discussions of mathematical models per se, for which I was most appreciative. Dr. Kellerer introduced the subject by indicating that he would address multihit models and exponential curves with the aim of answering the questions: (1) How good are biological data in supporting a linear-quadratic model of effect? and (2) Do biological endpoints reflect a quadratic dependence on energy transfer? In his discussion he made the assumption that at low doses, any dose effect relationship on autonomous cells must be linear, in those instances in which only a minor fraction of cells has been hit by a single charged particle. In this context, "autonomous effect" was defined as an effect on exposed cells which is independent of effects on neighbors. He offered the induction of chromosome aberrations as an example of linearity of biological response observed after exposure to low doses of sparsely ionizing radiation. He further noted that over a wider dose range both chromosome aberrations and cell killing display a linear-quadratic dose dependence after exposures to low-LET radiation. He indicated that in his opinion the observed linear-quadratic dose response after exposure to high dose rate low-LET radiation was more than a triviality or coincidence. With regard to linearity at low doses, he noted that the mathematical models had important pragmatic implications in terms of radiation protection, particularly

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since RBE for high-LET radiations increases with decreasing dose.

As further discussion of L-Q models, he reviewed the proximity theory of Lee and Sax, and noted that a second order process would lead to a quadratic (D^2) dependence on dose. For example, the formation of two-break chromosome aberrations depends on the occurrence of two separate lesions within a finite span of time. Whether interaction of two lesions can occur further depends on their proximity in space, or interaction distance. In order to have interaction, there must be close proximity or near neighbors of lesions. For low-LET radiations most lesions result from separate or independent tracts, whereas for high-LET radiations, single tracts may induce many "near neighbor lesions". The interaction distances for lesions was estimated to be approximately 1 in early work by Lee and Neary.

More recently, the data of Goodhead from irradiations of cells with soft X-rays and particles with short tract distances have suggested much shorter interaction distances. Goodhead has further concluded that a threshold energy is required for the induction of lesions. According to the PERS Theory more than 300 ev within 3μ meters is required for the induction of mutations. Less than 300 ev is reparable. Goodhead has also suggested that the phenomenum of repair saturation exists, such that with increasing radiation dose, the repair system can become saturated. As evidence to counter this theory, Kellerer offered information that for chromosome aberrations, repair times are not dependent on absorbed dose, and that for Erlich ascites tumor cells, there is no evidence of decrease in the rate of repair at high doses.

Regarding the linear-quadratic model which he champions, he then noted that recent data have suggested that there are different interaction distances for linear and quadratic functions, and that these distances are much longer for quadratic functions. Such distances would require the removal of large sequences of DNA, perhaps in the range of several thousand nucleotide pairs. He further emphasized that the quadratic process requires binary or dual action, and that the higher the dose, the more likely the probability of misrepair.

Considerable heated discussion followed Dr. Kellerer's presentation which reflects the current degree of controversy regarding the mechanism of action of radiation at the molecular level. Among several other comments made, Dr. Sheldon Wolfe, University of California at San Francisco, raised the issue that since double strand breaks in two spearate chromosomes are required for the

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formation of chromosomal exchanges, then the dose response curve in actuality reflects a fourth order process.

Several posters addressed the effects of radiations having differing LET on the induction of cytogenetic lesions in vivo or in mammalian cells exposed in vitro.

Douglas Grahn and his associates at Argonne National Laboratory presented results of an extensive series of studies on somatic and germ cell effects in mice exposed to low doses of fission neutrons and ^{60}Co gamma rays. Their major conclusions regarding genetic effects were (1) that protraction of low-LET radiation reduces the effect per rad, while protraction of the high-LET radiation does not reduce effectiveness and may significantly augment the effect per rad for some endpoints (2) RBE values are generally lower for genetic damage than somatic damage (3) for genetic damage RBE values are higher for effects induced in the stem cell than for injury induced in meiotic and post-meiotic cell stages. They concluded this finding reflects the intrinsic variation in the capability for DNA repair among different cell stages of the male germ line.

Julian Preston and his coworkers from Oak Ridge National Laboratory presented interesting information regarding mechanisms involved in the formation of radiation-induced chromosome lesions in cells exposed to high- or low-LET radiation. These authors have previously reported that post-radiation incubation of human lymphocytes with cytosine arabinoside (Ara-C) results in an increase in the number of radiation-induced dicentric chromosomes. They interpreted these results as suggesting that X-ray induced aberrations result from the misrepair of base damage, and not from directly induced strand breaks. In this report they presented data from recent studies in which human Go lymphocytes were exposed to fission spectrum neutrons and subsequently incubated in Ara-C. No potentiation of effect was observed which they interpreted as providing evidence that different molecular mechanisms are involved in the formation of two-break lesions after exposure of cells to high- and low-LET radiation.

Several posters addressed the cytogenetic effects of in vitro or in vivo alpha particle radiation in mammalian systems. Simmons and associates reported

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data from the in vitro exposure of confluent V-79 cells grown on a mylar base to alpha-particle radiation from a source plate of curium 242. Cells were harvested after 1.5 doublings. The dose response relationship for chromosome lesion induction was linear over a dose range of 0-150 rad with a coefficient of 3.2×10^{-3} dicentrics/cell/rad. Although interpretation of data from cultured fibroblasts that have possibly completed more than one cell division may be confounded by mitotic loss of lesion-bearing cells, it is interesting that these findings are in good agreement with the previously reported coefficients of Edwards et al. of 28.6×10^{-4} dicentrics/cell/rad obtained after the in vitro exposure of human Go lymphocytes to alpha particles from curium 242.

Tony Brooks and his associates from the Lovelace Inhalation Toxicology Research Institute reported a nice series of data on the retention, distribution, and cytogenetic effects of inhaled plutonium in nonhuman primates. A major point of their findings was that although they could detect an increase in radiation- induced aberrations in cultured lymphocytes from exposed rhesus monkeys, the level of effect was minor relative to the total accumulated dose to lung. Similar results were reported by Heinze and her associates in their analysis of chromosome aberrations in lymphocytes of Chinese hamsters after long-term exposures to incorporated alpha emitters. These animal data are contrary to our observation of a high frequency of lymphocytes with lesions in a chelated patient having an excessive body burden of americium 241, and suggest that the continuous mobilization of transuranics by DTPA may be a significant variable in comparing lymphocyte data from human and other mammals.

D. J. Chen, M. R. Raju and Tokita of Los Alamos reported findings of their studies of mutagenicity and DNA repair in human fibroblasts after exposure to alpha particles from an electroplated source of plutonium 238. Relative to X-rays, the RBE for mutations for alpha particles at 20% survival was 2.5. They concluded from their studies that normal human fibroblasts cannot repair sublethal damage induced by alpha particles, and that alpha particles may induce more damage leading to 6TG mutations than X-rays at equal survival doses.

Two papers reported observing increases in sister chromatid exchanges in marrow cells of animals exposed to both high- and low-LET radiations. J. L. Poncy and associates reported observing an increase in the frequency of sister chromatid exchanges from approximately 7 to 9 SCE/metaphase marrow cells in rats exposed to fission spectrum neutrons in doses of .32, .5, 2, 3, or 4 gray. Animals were perfused with 5-bromodeoxyuridine for 20 hr prior to the SCE analyses. It was interesting to note that although the authors observed significant differences in SCEs in marrow of exposed rats, they could not correlate the increase in SCEs with radiation dose.

In a second report on radiation-induced SCEs in vivo, Carsten and associates from Brookhaven reported increased frequencies of SCEs in marrow of mice after continual ingestion of tritiated water at a concentration of 3.0μ Ci/ml. After prolonged ingestion of tritiated water, a frequency of about 3.0 SCE/cell was observed in the irradiated mice vs. a frequency of about 2.75 SCE/cell in the control animals. An interesting aspect of this data was that SCE frequencies in mice did not appear to increase as a function of time on tritiated water, but rather that the SCE frequency in the control animals appeared to decrease with successive sampling. Although data from both these studies were interpreted by the authors as providing evidence that radiation of differing LETs is effective in inducing SCEs in vivo, certainly the effect if it exists, must be minimal.

Studies of variables affecting human genetic hypersensitivity

During the last several years we have evaluated mutagen-induced cytogenetic hypersensitivity in cells from patients with Down's syndrome, Ataxia telangiectasia, and Huntington's chorea, and in lymphocytes of a primate species at apparent genetic risk for colon cancer.

A number of posters presented at Amsterdam addressed various questions regarding factors affecting the expression of genetic hypersensitivity in human cells.

Nancy Oleinich and her associates from Case Western Reserve reported that AT-lymphoblastoid cells show less mitotic delay after exposure to X-radiation

or Bleomycin than do normal lymphoblastoid cells, and postulated that the relative lack of delay in S and G_2 may be due to a single genetic alteration. Earlier studies by other investigators have suggested that the observed hypersensitivity of AT cells in terms of X-radiation induced chromosome damage results from the fact that, as a result of the lack of delay, AT cells have a shorter period of time in which to repair lesions.

Vijayalaxmi and Evans reported results of their assessment of mutagen-induced chromosome aberrations and SCEs in lymphocytes of a patient with Friedreich's Ataxia, a human genetic disease similar to AT. They observed normal baseline SCE frequencies, and hypersensitivity in the induction of chromosome aberrations after exposure to radiation, as has previously been reported for patients with AT. An interesting observation was that in contrast to earlier reports in AT patients, lymphocytes from the individual with Friedreich's Ataxia were also hypersensitivie to the induction of SCEs after in vitro exposure to mitomycin C and EMS.

Ejima, Sasaki and associates presented data from an extensive study of cellular radiosensitivity in dominantly inherited diseases predisposing to cancer. The authors evaluated X-ray induced cell killing after exposures to 0-1000 rad in cell strains from patients having familial, sporatic or D-deletion (chromosome 13) retinoblastoma, familial polyposis, and Ataxia telangiectasia. Increased sensitivity to cell killing effects of X-radiation was only observed in the AT cell strains. None of the strains derived from patients having a structural deletion, functional deletion, or triplication of the postulated "repair locus" on human chromosome 13 expressed enhanced radiosensitivity.

Murnane and Painter of the University of San Francisco reported results of an evaluation of major structural proteins in fibroblasts of patients with Ataxia telangiectasia. In their analysis they failed to identify protein irregularities in AT fibroblasts in either histone, chromatin or nuclear matrix.

Studies of germ cell effects in various mammalian species

The subject of genetic and/or cytogenetic effects in germ cells was

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discussed in a semi-plenary and introductory lecture, as well as in several posters.

Dr. K. Sankaranarayanan of the University of Leiden, The Netherlands, presented a semi-plenary lecture entitled "Radiation Induced Mutational Damage in Mammals", which was primarily a historical review of studies in radiation mutagenesis. He noted that in the 1950's to 1960's a great deal of work established basic premises for radiation-induced genetic changes in mammals including (1) verifying that mouse genes are more radiosensitive than genes in prokaryotes (2) establishing the effects of radiation dose, dose rate and fractionation on mutation induction in mammalian spermatocytes and oocytes and (3) in determining the effects of interval between radiation and time of conception on the expression of mutations in irradiated female mice. During the 1960's the kinetics of aberration induction in human chromosomes were elucidated, with continued work on the nature and mechanisms of radiation-induced mutations and aberrations, and on radiation-induced specific locus mutations in mice. Regarding the correlation between radiation-induced chromosome lesions and mutations, he noted that depending on the stage of the cell cycle irradiated, a sizable portion of radiation-induced mutations (14-78%) are associated with chromosome deletions. For mutations involving the HGPRT locus in human fibroblasts about 5-10% of those induced after exposure to X-ray, 20% by helium ions and approximately 60% of those induced after exposure to alpha particles are associated with aberrations.

He noted that there is still some unresolved controversy regarding whether mutations result from single tract events (Russell) or from the interaction of 2-tract events (Abrahamson and Wolfe), but that there is ample scientific evidence that chromosome lesions result from DNA double strand breaks. He spent some time discussing dose response relationships for the induction of specific locus mutations in male and female germ cells at differing stages of development, and reviewed dose rate reduction factors for specific locus mutations in spermatogonia and oogonia. Lastly, he addressed current work in defining molecular lesions including defective excision repair in xeroderma pigmentosum, and work aimed at defining biochemical defects in other recessive diseases including Ataxia telangiectasia, Bloom's syndrome, etc. He noted that with the exception of XP, no firm evidence for specific biochemical defects has been gleaned from these studies. However, recent work has suggested that human chromosomes 3 and 14 may be important in the repair of UV damage. (Peter

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Lalley and his associates from ORNL presented a poster on these data at the meeting.) In closing, he noted that more future work is needed on oocyte cytogenetics, and in the area of translocation studies in male spermatogonia.

In addition to the lecture by Dr. Sankaranarayanan, Dr. A. G. Searle of the Medical Research Council, Harwell, presented a nice overview paper entitled "Some growing points in mammalian radiation cytogenetics". He introduced the topic of genetic risks by noting the various types of genetic damage that may be incurred, including (1) changes in chromosome number and structure, (2) chromosome deficiencies, and (3) dominant and recessive gene mutations. He noted that work being done on radiation-induced non-disjunction is still very controversial, but that recent studies based on work done on procleavage divisions in the female mouse have shown increases in non-disjunction resulting in hyperdiploidy. Regarding structural lesions he noted that Robertsonian translocations are induced rarely if at all in mammals other than man, rather the primary structural lesions induced by radiation are reciprocal translocations which can be assessed in spermatogonia or oogonia by scoring rings of 4. One of the major problems in assessing risk is how to get from observed frequencies of induced translocations in gonia to predictions of risk.

In this context, he addressed several factors that must be taken into consideration when estimating risk.

1) relative radiosensitivity

2) extrapolation to low doses

3) rate of transmission of damage to zygote

4) proportion of conceptuses that survive to birth with viable imbalances in their genome

5) proportion of gametes affected

Regarding radiation sensitivity, he addresssed contradictory findings of the rate of translocation induction in marmoset and man (Brewen and Preston), the crab-eating monkey, and rhesus monkey (Mary Lyon and van Buul). Based on reported results in these species, man and marmosets appear to be quite sensitive to the induction of translocations, the rhesus monkey relatively insensitive, and the crab-eating monkey intermediate. He noted that there is still some question as to why man and marmoset are higher than other primates,

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and that additional work is needed on translocation induction in spermatogonia to resolve the issue.

In relation to effects at low doses, he indicated that studies in mice exposed to 10 rad per day for 60 days beginning at conception had shown that one observes a much lower yield of translocations after irradiation of embryonic stages. Similarly, the observed effects at doses of 0-5 rad are lower than those predicted by extrapolation from the $\alpha D + \beta D_2$ model for lesion induction. Thus, the risk at low doses may be considerably less than that expected based on studies at high doses and dose rates.

In addition to the reduced frequency of lesions induced after exposure to low dose radiation, Dr. Searle discussed the further reduction in gametes bearing structural aberrations as a result of segregation and pre- and post-implantation loss. For lesion classes involving single events, one expects a transmission of only 25% after meiotic segregation, which is further reduced by a factor of 2 after implantation losses, resulting in a total transmission of 1/8 (work of Ford and Searle). Generoso has reported a similar reduction by a factor of 2 at all doses studied except 150 rad in which he observed the predicted number of translocations. He noted that other work has recently shown that translocation bearing gametes are delayed in passage through diakinesis. With regard to viability of gametes bearing structural lesions, he indicated that earlier studies have suggested about 6% of conception products with unbalanced translocations are viable, whereas later studies employing in vitro cell systems show a higher percent viability.

Translocations Yielding Viable Imbalance

Percentage Induced	Percent Products with Viable Imbalance	Reference
5	25% of all unbalanced	BEIR (1980)
-	6% of all unbalanced	UNSCEAR
40	Half of all unbalanced	Dutrillaux (1981, 1983)

Dr. Searle's presentation was of particular interest to me since our laboratory has for several years been involved in studies of the rate of transmission of chemically induced structural lesions in oogonia to pre- and post-implantation rabbit embryos. One topic not addressed by Dr. Searle was the utility of induced aberrations in somatic cells as a predictor of the rate

of transmission of unbalanced translocations to the products of conception.

Several posters also addressed the relative sensitivity of mammalian germ cells or early embryos to radiation-induced lesions. Jacquet and Leonard reported results of their evaluation of differential radiosensitivity of the male and female pronuclei in the mouse zygote. Following in vitro irradiations they observed that chromosome aberrations are equally distributed between the male and female pronuclei. Based on these results they suggested that previously reported differences in radiosensitivity of somatic cells of various mammals is probably not related to differences in nuclear volume.

Yamada and associates from the National Institute of Radiological Sciences, Chiba, Japan presented interesting data on the differential sensitivity of mouse zygotes to radiation at various times after in vitro fertilization of ova. The authors used blastocyst formation to quantitate radiation effectiveness during the first 12 hours after fertilization . They observed relatively low sensitivity shortly after sperm entry, extremely high sensitivity (LD-50, 40R) at the beginning of pronuclear development (4-6 hr after fertilization). In the later pronuclear stage (12 hr) the sensitivity again became low (LD-50, 400R). They also noted variability in the frequency of radiation-induced chromosome aberrations in first-cleavage metaphases after irradiation of zygotes in the early vs late pronuclear stage. These authors concluded that such in vitro systems can provide an excellent method for assessing changes in radiation-sensitivity of the pronuclear mouse embryo during the complete cell cycle.

That the ability of mammalian ova to repair UV-induced genetic damage may depend on the strain of female mouse was suggested by the studies of Pedersen and Bennett. These authors assessed SCE frequencies in embryos of three mouse strains by fertilizing ova in vitro with UV-irradiated spermatozoa. The fertilized eggs were allowed to proceed through one round of DNA synthesis in the presence of BrdU. They observed significantly different SCE frequencies (14-fold) after fertilization of ova from Balb/C, Dub, and C57 black mice, and concluded that the differences may be related to strain specific differences in repair capabilities.

An interesting paper that is already generating some discussion on estimation of genetic risk in the male was presented by P. W. W. van Buul. This author presented data on the induction of translocations in stem cell spermatogonia of rhesus monkeys exposed to 25 to 400 rad radiation. He observed that both dose response and dose fractionation effects in the rhesus monkey were quite different than previously reported data in the mouse, although histological findings were quite similar in rhesus monkey and man. Likewise, the incidence of translocations in the rhesus monkey spermatocytes was approximately 10-fold lower than that previously observed in the marmoset. The reasons for the discrepancies in the observed effects in different species are not clear, but suggest that additional studies will be required to resolve the risk of male germ cell exposure.

In addition to these various papers which I considered directly relevant to ongoing work in our laboratory, I would like to give a synopsis of two additional lectures that were relevant to my work on NCRP Committee 40. On Tuesday morning, Dr. M. M. Elkind (Past President of the U. S. Radiation Research Society) presented an excellent overview of repair mechanisms in radiation-induced cell transformation. Although Dr. Elkind is currently in the Department of Radiology and Radiation Biology at Colorado State University, much of the work he discussed had been conducted during his earlier tenure at the DOE Facility at Argonne National Laboratory. Dr. Elkind introducted his lecture by noting that appropriate in vitro mammalian cell systems facilitate the study of cellular mechanisms of radiation oncogenesis. For work conducted at Argonne, he and his colleagues employed the mouse embryo derived C3H 10T1/2 cells for studies of the effects of protracted radiation exposures on cell killing and the incidence of neoplastic transformation. These cells normally exhibit contact inhibition in monolayer cultures, but after neoplastic transformation will form foci (colonies) of densely packed, disorganized cells that can be readily identified by appropriate staining procedures. Cells from such foci give rise to fibrosarcomas when injected into C3H mice. For studies of the effects of radiation quality and protraction on the incidence of induction of transformed cells, monolayers were irradiated and 150 viable cells inoculated into petri dishes. Dishes were assayed for colonies at the end of five weeks. For studies of cell survival, 80 cells were inoculated and assayed

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after 14 days. Dr. Elkind summarized data from several studies, and noted the following relevant conclusions:

1) potentially transformed cells exhibit the same sensitivity as other cells in terms of cell killing

2) the expression of transformation in irradiated cells depends on two concurrent phenomena, i.e. the induction process as modified by cell killing, so that the observed dose response reflects the combination of the two processes

3) cells can repair sublethal damage when doses of low-LET radiation are delivered at low dose rates

4) in addition to repair of sublethal damage, cells can also repair "sub-transformation" damage after exposure to low dose rate low-LET radiation

5) in contrast to low LET radiation, protracted exposures of fission spectrum neutrons (Janus reactor at Argonne National Laboratory) result in the significant enhancement of the frequency of transformation in the low dose regions, while cell survival is essentially unchanged relative to that observed after a single dose delivered at a high dose rate.

Dr. Elkind noted that data presented in a recent report by Goodhead (which will be published within the next few months) was relevant to the discussion of neutron effects. At doses of 0 - 10 rads, 82% of the irradiated cells are not "hit" following exposure to fission spectrum neutrons, and of those that are hit, 90% are single hits while only 10% are double hits.

He concluded by noting that tumorgenesis probably depends on two factors:

1) cell transformation x cell survival

2) repair in target cells

He also stressed that studies at Argonne suggest that effects are autonomous, i.e. on single cells, and that interaction of cells is not required in transformation. This viewpoint is currently controversial since work at Columbia University suggests that interaction of lethally irradiated and non-lethally irradiated cells is necessary for transformation.

In my opinion, the most interesting aspect of the studies with 10T1/2 cells is the observation of enhancement of transformation after protracted exposures to fission spectrum neutrons, which Dr. Elkind has interpreted to be the result of a net "error-prone" repair of transformational damage. The possibility of "potentiation" of effects of neutrons after protracted exposures raises questions regarding establishing safe limits of permissible exposures

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for workers in the atomic industry, and such information must be considered. However, it seems to me that considerable additional work with in vitro transformation systems is needed to validate findings and to resolve points of controversy in data reported by major research groups at Columbia, Harvard, and Argonne.

Lastly, Dr. Gil Beebe of the National Cancer Institute delivered a nice overview of variables that affect radiation carcinogenesis in man. He introduced the talk by raising the question, "Is radiation a general carcinogen?" and noted that extensive data have shown that chronic lymphocytic leukemia and Ewing's sarcoma are not induced by radiation. Of the cancers that are known to be radiogenic, such as thyroid cancer, cancer of the bone marrow, and breast, most is known about thyroid cancer. In each of these cancers the induced incidence is quite different from the natural incidence at specific sites. He suggested that a variable that should be considered is the possibility that there may be differences in sensitivity of different tissues and sites. Regarding dosimetry he stressed that mean tissue doses are obviously more meaningful than skin doses, and that even with specific tissues, all cells may not be target cells. He suggested that some of the variations in risk estimates may be related to how dose is calculated. In terms of the impact of radiation quality on risk in man, he indicated that currently very little is known of the effectiveness of neutrons, especially in light of the recalculation of dose in the Hiroshima A-Bomb survivors. Likewise, more information is needed on I-131 in relation to its importance in nuclear reactor accidents. Another factor that should be considered is threshold. Studies in animals have suggested that there is a threshold for cancer induction in some sites. Also, there may be subpopulations of humans with increased radiation sensitivity. Studies have shown that heterozygotes for the AT gene are widespread in the human population. The possibility that there may be human subpopulations with genetically determined hypersensitivity is a confouning variable when trying to derive estimates of risk. He also noted that some studies have suggested that all leukemia may be the result of exposures to background radiation but cautioned that such data may be quite confusing if population sizes are not large enought to obtain accurate statistical data. Brief mention was also made of the variable dose rate. NCRP Committee 40, of

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which I am a member, had concluded in Report 64 that, based on a number of biological systems, the best estimate of a DREF (dose rate reduction factor) is 2-10. However, the only human data for comparing the effects of dose rate in cancer induction in human populations suggests that no reduction in risk for breast cancer can be demonstrated after fractionation of doses (TB series vs data from A-Bomb survivors). Another important variable in assessing the carcinogenicity of ionizing radiation is the time response for expression of cancer. Although biological determinants are not clear, it has been observed that for solid tumors the appearance of malignancy is inversely related to age at time of exposure. The younger the person at the time of exposure the later the cancer appears. For some cancers, i.e. cervical cancer, expresssion continues until the end of life. In general, the latency period depends on dose. Also important in the expression of radiation induced cancers are a number of host factors. Age is a primary determinant of risk. For example, studies have shown that cancer is increased after pelvic radiation of the fetus. Thus, the fetus may be highly radiosensitive. Also, sex, race, hormonal status may influence the expression of radiogenic cancer. This has been amply demonstrated in experimental animal systems. Also, there is some current controversy on risk projection models, whether one should view data in terms of relative or absolute risk. Certainly this lecture clearly demonstrated the complexities involved in conducting epidemiological studies in attempts to quantify the carcinogenic risk of exposure of human populations to ionizing radiation.

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Overall Critique:

As I noted in the introductory paragraphs of this trip report, I considered the 7th International Congress to have been well-planned and well-organized, and the facilities at the RAI generally excellent. The attendance was good, and included a large number of well-qualified participants from many countries. As with any large meeting, the quality of science presented in the proffered papers varied considerably from excellent to mediocre, but generally was good. Likewise, the lectures presented by the invited Semi-plenary and Introductory Speakers were for the most part thought-provoking and well-presented by highly recognized specialists in several respective fields.

My primary criticism of the scientific organization of the meeting relates to the format of presentation of the proffered papers. Although I am sympathetic with the dilemma of the Program Committee in deciding how to most effectively organize a program that included in excess of 1000 presentations, I personally did not like the poster-workshop format. The primary reasons for my dissatisfaction are as follows. Although we had been given specific instruction regarding design, size of type, lay-out etc. of posters well in advance of the meeting, many of the presentations were illegible (for those of us with bifocals), much too detailed, or not nearly detailed enough. Because posters were on display for only a few hours on one day, frequently there were large crowds milling about which made it difficult to get close enough to be able to read the material, and even more difficult in concentrating on important technical details. Another problem, that may have been somewhat unique to my research area of interest, was that papers related to human and experimental cytogenetics were widely scattered and assigned to several different sessions, including B2. DNA damage and repair in cells; B4. Mutagenesis and chromosome changes; C4. Genetic effects; E3. Biological indicators, etc., resulting in confusion in selecting which introductory speaker/rapporteur sessions to attend. I'm not certain what positive recommendations I could make for improving the format, since scheduling 1000 ten-minute talks would also present numerous problems with overlapping of sessions. One alternative would be to restrict the number of proffered papers accepted for presentation, and possibly to schedule a number of workshop sessions on topics of specific interest. Or if the poster-format should be maintained, it would be helpful if the posters were left standing for a longer period of time so that the number of participants trying to read the material

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at any one time might be reduced. Also, the poster-workshop format could be improved considerably if all participants could glean information relative to how to effectively present scientific information in that specific format.

For me personally, the most positive aspect of international meetings of this caliber is that such gatherings tend to bring together a number of scientists from different countries who rarely have the opportunity to meet and discuss first-hand ongoing work of mutual interest. In highly specialized fields such as human radiation cytogenetics there are relatively few scientists who are actively invovled in similar research activities. Having the opportunity to meet persons whose work is primarily known via the literature, tends to promote long-term communications as well as to provide a forum for seeking timely information on specific points of current agreement or disagreement. To mention just a few contacts made in Amsterdam, it was certainly very beneficial to me to have the opportunity to discuss several aspects of our ongoing dosimetry/radiation research program with David Lloyd of the NRPB, Jan Tawn of British Nuclear Fuels Limited, David Scott of the Medical Research Council, and Bauchinger of the Federal Republic of Germany. Likewise, I was pleased to be able to meet Honda and Tanada of the Radiological Institute in Japan, and to establish the groundwork for future exchange of information on long-term follow-up studies in persons with previous radiation exposures. Similar meaningful contacts were made with a number of cytogeneticists whose primary interests are in the areas of genetic hypersensitivity and germ cell effects. In addition to the benefits I personally gained from discussions with participants who presented data, I believe our efforts at REAC/TS were fostered in the international community by our presentation of a portion of our work in the session on dosimetry. Our poster was well-received and viewed by a number of persons whose interests ranged from defining the RBE of alpha particles to assessing in vivo effects of transuranic contaminations in nuclear workers. The cytogenetic data that we have obtained on the heavily contaminated Hanford americium accident survivor is unique, and was viewed with interest by a number of participants.

Overall, I was impressed with the quality of the science presented at the International Congress, and pleased to have had the opportunity to attend and participate.

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Technical Committee Meeting on "Medical Handling of Over-exposed Persons"

At the invitation of Dr. A. Bianco, Scientific Secretary, IAEA, On July 11 and 12 I participated in a Technical Committee Meeting on "Medical Handling of Overexposed Persons". The meeting was held at IAEA Headquarters, at the Vienna International Center on the outskirts of Vienna.

The Technical Committee was assembled by IAEA to discuss the subject material to be included in a series of forthcoming manuals the IAEA hopes to produce for distribution to physicians in both developing and developed countries. The Committee consisted of invited participants from nine different countries:

Mr. Dan Beninson
C.N.E.A
Buenos Aires, Argentina

Mr. Emil Kunz
Institute of Hygiene and Epidemiology
Prague, Czechoslovakia

Mr. L. Ohlenschlaeger
Medizinische Abteilung
Fed. Rep. of Germany

Mr. Henri Jammet (Chairman)
C.E.A.
Fontenay-aux-Roses, France

Mr. V. R. Shah
B.A.R.C.
Bombay, India

Mr. Yukio Tateno
National Institue of Radiological Sciences
Chiba, Japan

Mr. G. B. Schofield
British Nuclear Fuels, Ltd.
Seascale, United Kingdom

Mr. Ivan Simonovic
Klinicki Centar Bolnicki
Yugoslavia

In addition, Dr. N. T. Racoveanu, Chief, Radiation Medicine, World Health Organization was in attendance. Dr. Henri Jammet, of the French Commissariat à

l'énergie atomic served as Committee Chairman.

All participants convened at 9:00 hrs on Monday morning, and Dr. Bianco explained in detail the charge of the Technical Committee: that IAEA wishes to produce two or more publications addressing (1) the medical and biological assessment of human radiation and (2) the medical criteria for treatment of overexposed persons. The first volume would deal with theoretical considerations and medical principles regarding diagnosis and prognosis of radiation injury, and would be published as an IAEA Brown Safety series booklet. One or more additional guides would be published as Blue Series documents, which are manuals or "how to" booklets addressing specific medical criteria for treatment. It is IAEA's intent that the manuals contain information relevant to the needs of both the "educated" physician, and of physicians having no previous training in radiation medicine. Dr. Bianco invited the participation and co-sponsorship of the WHO in this venture, and Dr. Racoveanu voiced his support.

During the next two days a general subject outline was developed for material to be included in the publications. After considerable discussion, it was agreed that the Brown Safety Series Volume should address the General Principles of Diagnosis, Prognosis, and Treatment of Over-exposed Persons and should discuss several theoretical considerations that face physician's dealing with persons with potential radiation injury, including:

1. Types of over-exposure and Definition of exposure (2 x ICRP limits)
2. Mechanisms of Radiation Action
   a. Stochastic effects
   b. Non-stochastic effects

(Forthcoming recommendations of ICRP Committee I would be used in this section).

3. General Principles of Diagnosis

   Immediate Actions to be Taken by Physicians

   a. Collection of exposure information (detailed patient history)
   b. Initiation of decontamination if necessary
   c. Treatment of traumatic injury has first precedence (there was considerable discussion on the need for obtaining accurate information on the accident scenerio and it was decided that a series of questions that a physician might use in history taking would be helpful).

4. Measurements of Effects of Damage

   a. Discussion regarding tests for physiological functions and

   b. Morphological changes

5. Principles of Treatment

   a. External Exposure

Discussion of first action to be taken in instances of external exposures. (For example, in instances of localized exposures, the text should address the question "If the physician observes this specific symptom-take this action".) It was recommended that the instructions also note "what not to do". Several theoretical points should be discussed including contrasting radiation and chemical burns, the need for assessing dose and dose distribution and highlighting the time course evolution of symptoms for both partial body and whole body exposures.

   b. External Contamination

The key points to be addressed should include 1) the assessment of whether contamination is present 2) actions to be taken (wash exposed area, save first wash sample etc.) 3) guard against internal contamination of patient and cross-contamination of medical or emergency personnel.

   c. Internal Contamination

Should present rationale for medical management of internally contaminated patients, key point: treat life-threatening situation first, then proceed with decontamination.

In addition to formulating an outline for the Brown Safety Series Document, there was considerable discussion of what information should be included in the Blue Series Manuals. It was generally agreed that at least three manuals would be needed initially, including Instruction Manuals on (1) Assessment and treatment of external exposures and internal contaminations, (2) Biological dosimetry methods and (3) Physical dosimetry methods. Dr. Bianco presented to the Committee an outline of a Blue Book on Biological Dosimetry that is currently under formulation.

During the two days that I participated, the Committee made rather slow but substantial progress in formulating an outline for the Brown Series Publication. I was impressed at the impact that earlier work at the Medical and Health Sciences Division, and REAC/TS have deservedly had on such

international meetings. On numerous occasions reference was made to usefulness of ICRP Publicatin 28 on The Principles and General Procedures for Handling Emergency and Accidental Exposures of Workers to which Dr. Gould Andrews contributed; to IAEA Series #47 Manual on Early Medical Treatment of Possible Radiation Injury to which Dr. C. C. Lushbaugh made considerable contributions, and to our REAC/TS Conference Proceedings on The Medical Basis for Radiation Accident Preparedness edited by Drs. Karl Hubner and Shirley Fry. Although my primary contribution to the Committee was to offer commentary regarding cytogenetic methods for assessment of dose, I personally benefitted from the general discussion, and hope that some of the information that I gleaned will be of use to other staff members at REAC/TS.

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APPENDIX A

SIX YEAR CYTOGENETIC FOLLOW-UP STUDY OF AN INDIVIDUAL HEAVILY CONTAMINATED WITH AMERICIUM 241

AUTHOR'S NAME 2nd LINE BELOW TITLE

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[1]Oak Ridge Associated Universities, Oak Ridge, Tennessee and [2]Hanford Environmental Health Foundation, Richland, Washington, U.S.A.

Begin ch In August of 1976 a 64 year-old nuclear chemical operator was heavily contaminated with Americium 241 resulting from a chemical explosion of an ion exchange column. On that day it was estimated that about 3000μCi of Am-241 had been deposited on his face with an additional 300μCi embedded in the facial skin. He received extensive chelation therapy with DTPA, and by 24 months after the accident had excreted > 1000μCi Americium in urine and feces. Details of the accident and of the patient's medical management and clinical course have been presented elsewhere (1). Cytogenetic evaluations in cultured lymphocytes from this patient have been conducted by our laboratory in Oak Ridge and by investigators at the University of Pittsburgh (2). In this report we summarize results of the Oak Ridge Studies.

Thirty days after the accident we initiated 50hr lymphocyte cultures on-site at Hanford to determine whether cytogenetic evidence of in vivo exposure to α-particles could be detected. In the analysis of 179 metaphases we observed that 33 had typical radiation-induced chromosome lesions, with about half the damaged metaphases exhibiting multiple 2-break aberrations. We considered these observations significant because of the paucity of published data on cytogenetic effects in lymphocytes of persons internally contaminated with transuranic elements. At 92 days after the accident we conducted studies to determine whether any variables in our culture system would affect the recovery of lymphocytes bearing α-radiation-induced chromosome lesions. In this series of experiments we observed: (1) no significant differences in the types or frequencies of aberrations in cultures initiated on-site compared to data from cultures initiated from blood shipped to Oak Ridge (2) no difference in aberrations between 50hr micro vs. macro cultures (3) a significant decrease in aberrations in cultures harvested at 52 vs. 50 hours.

Subsequently, we have analyzed radiation-induced chromosome aberrations in 48-50hr lymphocyte cultures from 10 additional shipped blood samples. The highest frequency of cells with centric rings and di- or multicentrics (i.e. 24%) was noted in cultures initiated 3 months after the initial contamination. During the 17th through the 39th month only 8-10% of the metaphases examined had asymmetrical lesions. In the sample obtained at 39 months we initiated bromodeoxyuridine-substituted cultures to allow selective analysis of metaphases in their first in vitro division, and observed lesion frequencies comparable to our findings in the 33 month culture which did not contain BrdU. Beginning at 47 months we have observed an apparent increase in both the percentage of metaphases bearing centric rings and multicentrics and in the relative numbers of lesions in the damaged cells (Table 1). In addition to scoring aberrations, we analyzed sister chromatid exchanges in 2nd division metaphases in 72hr BrdU-substituted cultures at 10, 20 and 35 months, and in 49-50hr cultures at 47 and 53 months. SCE frequencies were not elevated above control levels in any culture.

Table 1. Cytogenetic findings in lymphocytes from ^{241}Am accident victim.

Month	Cells Scored	% Cells with* Lesions	% Cells with Rings and Dicentrics	Ring and Dicentric Equivalents/100 Cells
1	173	19.0	14.5	27
3	200	31.5	24.0	46
10	300	22.4	18.0	35
17	200	9.5	8.0	16
20	200	10.5	8.5	12
25	200	10.5	7.5	12
33†	200	13.0	9.0	16
39†	220	15.4	10.0	14.5
47†	75	26.7	16.0	38.7
53†	200	31.5	22.5	40.5
56†	100	20.0	16.0	43.0
62†	162	18.0	13.6	22.8

* Excluding gaps and chromatid breaks.
† Lesions in 1st division metaphases from BrdU-substituted cultures.

In all cultures a characteristic observation is that many of the radiation-damaged metaphases exhibit multiple 2-break lesions. To determine whether the observed distribution of dicentrics differed from that expected based on Poisson statistics, we calculated probabilities based on unit normal deviate values. In all cultures the observed distribution was significantly ($p < .001$) overdispersed relative to the Poisson expectation. (Table 2)

Table 2. Example of distribution of dicentrics (data from 53mo culture).

				Cells with No. of Dicentrics							
# Dicent	# Cells	$\bar{X}$		0	1	2	3	4	5	6	
72	200	.360	Exp.	139	51	9	1	0	0	0	$p < .001$
			Obs.	156	30	7	3	2	1	1	

Our data show that cytogenetic evidence of in vivo exposures to α particles can be detected by scoring aberrations in cultured lymphocytes of persons heavily contaminated with Am-241, and that overdispersion of 2-break lesions is a characteristic finding. Our observation of a gradual decline in the number of radiation-damaged metaphases during the 17th through the 39th month, and a subsequent increase in lesion bearing cells during the 4th and 5th year after the initial contamination was unexpected. Presently, we have no explanation for this observed pattern, but it appears that factors other than lymphocyte turnover and cumulative whole body dose are affecting the cytogenetic findings.

ACKNOWLEDGEMENTS

1. Heid, K. R., Breitenstein, B. D. et al. The 1976 Hanford Americium Accident, in Medical Basis for Radiation Accident Preparedness, K. Hübner and S. Fry, ed., N.Y., Elsevier, N. Holland, 1980, pp. 345-355.
2. Dr. Neil Wald and Sylvia Pan, University of Pittsburgh.

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APPENDIX B

ITINERARY FOR DR. L. GAYLE LITTLEFIELD

AMSTERDAM-VIENNA TRIP

7/1/83 - 7/16/83

July 1, 1983	Left Clinton home for Atlanta, GA		2:00 p.m.
July 1, 1983	Left Atlanta, GA	# 18	9:30 p.m.
July 2, 1983	Arrived London, England		10:15 a.m.
	Left London	B. Caledin # 818	11:15 a.m.
	Arrived Amsterdam, The Netherlands		
July 2-8, 1983	Attended 7th International Congress Radiation Research		
	Hotel: Eurocrest, De Boelelaan 2, Amsterdam		
July 9, 1983	Left Amsterdam	KLM # 809	12:50 p.m.
	Arrived Vienna, Austria		
	Hotel: Astoria, 1010 Wien, Kartner 32, Vienna		
July 11-12, 1983*	Attended International Atomic Energy Agency Meeting		
July 15, 1983	Left Vienna	KLM #258	11:20 a.m.
	Arrived Amsterdam		1:05 p.m.
	Hotel: Ibis, Amsterdam		
July 16, 1983	Left Amsterdam	B. Caledin #811	10:15 a.m.
	Arrived London		10:15 a.m.
	Left London	Delta #11	12:15 p.m.
	Arrived Atlanta, GA		5:30 p.m.
	Arrived Clinton, TN		9:00 p.m.

* Traveler on annual leave July 13, 14, 15, 1983.

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