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FOREIGN TRIP REPORT

ORNL/FTR-3846

DATE: December 14, 1990

SUBJECT: Report of Foreign Travel of R. J. Michael Fry, Section Head, Biology Division

TO: Alvin Trivelpiece

FROM: R. J. Michael Fry

PURPOSE: To take part in an international conference entitled **Radiation Carcinogenesis in the Whole Body System** as a member of the organizing committee and to give the summary, December 4-6, 1990.

To visit the National Institute of Radiological Sciences at Chiba and present a talk on **Late Effects of Radiation**, December 7, 1990.

SITES VISITED: 12/4-6 International Conference Tokyo, Japan
12/7 National Institute of Radiological Sciences Chiba, Japan

ABSTRACT: The objectives of the trip were: (1) to take part in and to give the summary of a Symposium on Radiation Carcinogenesis at Tokyo, and (2) to give a talk at the National Institute of Radiological Sciences at Chiba. The breadth of the aspects considered at the conference was about as broad as is possible, from effects at the molecular level to human epidemiology, from the effects of tritium to cancer induction by heavy ions. The events induced by cancer that lead to cancer and the events that are secondary are beginning to come into better focus but much is still not known. Interest in suppressor genes is increasing rapidly in the studies of human tumors and many would predict that the three or four suppressor genes associated with cancer are only the first sighting of a much larger number.

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The International Symposium was held in the International Hall Foundation for Cancer Research at the National Cancer Center. The distinguished President of the Center, Dr. T. Sugimura, was a very active participant in much of the meeting. There were 26 speakers, mostly from Japan and the U.S. The Symposium was divided into six sessions: (1) Human Cancer after Exposure to Radiation, (2) Developmental Stage-dependency, (3) Experimental Radiation Carcinogenesis, (4) Cellular Aspects in Radiation Carcinogenesis, (5) Radiation Carcinogenesis in the Skin, and (6) Tumor Suppressor Genes and Oncogenes.

ORNL was well represented by alumni from both Japan and the U.S., Drs. Kondo, Yokoro, Sado, Nettesheim and Ullrich.

The opening address was given, appropriately by S. Kondo (Kinki Univ.). He discussed possible models that might apply to the multi-event process of radiation carcinogenesis. He suggested that dose responses for acute and chronic myeloid leukemia in the atomic bomb survivors differed, the latter having a threshold. In the case of acute myeloid leukemia, mutations of proto-oncogenes in hematopoietic stem cells could explain the response. The presence of a threshold response in chronic myeloid leukemia suggested that radiation acted on the stage operationally known as progression.

Kondo thought that high doses of radiation caused a persistent disturbance in the cell renewal system. The implication was that radiation induced some cancers only at high doses above a threshold value by killing a critical number of stem cells. He proposed that the opening statement to the Symposium should be that carcinogenesis was not just the problem of a single cell but also of the society of cells.

The session on radiogenic human cancer was opened by the doyen of the study of human radiation leukemogenesis, Dr. Ichimaru (Atomic Disease Institute, Nagasaki). His contention of not only a threshold dose for chronic myeloid leukemia but also for an even larger threshold for acute myeloid leukemia is at odds with the analyses made by most biostatisticians. Dr. Ichimaru and his colleagues have not embraced the new DS86 dosimetry which has altered the apparent dose-response relationship. Ichimaru thought the chronic myeloid leukemia was the most characteristic radiogenic leukemia and the incidence was higher in Hiroshima than Nagasaki. The explanation of this city difference remains unexplained. Is it related to differences (1) in the de novo incidence of chronic myeloid leukemia between the cities (this is not considered to be significant), (2) the age distribution, (3) other constituent factors such as viral sequences, or (4) a higher neutron dose than is suggested by DS86. Perhaps a fifth possibility, which is still unidentified, should be included.

It was suggested that slopes of the plots of relative risk as a function of dose increased in the following order, in terms of the types of leukemia: acute myeloid leukemia, acute lymphocytic leukemia, and chronic myelogenous leukemia.

Van Kaick (Heidelberg, FRG) and Mori (Chiba) discussed the late effects of thorotrast. There are a number of examples of iatrogenic cancers that have occurred, sadly, in sufficient numbers to make them valuable populations for epidemiological study. The cancers caused by the contrast medium thorotrast are an example. The results of the followup of German and Japanese patients have many similarities. Liver cancer predominates, with an incidence of over 400 cases in the German series of 2326 patients. In about 75% of the cases of the Japanese study the injections were associated with diagnosis of injuries incurred in the 2nd World War. In one subsample, 56 liver cancers were found out of 262 cases inspected. Van Kaick noted that brain tumors occurred as early as 3 years after carotid artery injections, leukemias after 5 years with 1.7:1 male-female ratio. One out of ten of the leukemias was chronic myeloid leukemia; lymphocytic leukemia was not increased but multiple myeloma was. A striking finding in the Japanese series was that about 23% of the cases had 2-4 different types of malignancies.

In neither series is there evidence of excess of small cell lung cancer. The most frequent liver tumors were carcinomas but about 35% of the tumors were hemangiosarcoma, a rare tumor. Cirrhosis appears to be found more frequently in the Japanese series.

The effects of levels of radiation that are in the range of environmental doses are well nigh impossible to study as the size of the populations required is enormous. Attempts have been made to study people exposed for their lifetime to doses from background radiation that are in excess of the average background radiation level; one of a U.S. population and at least two in other parts of the world but without success. Some years ago, Frigerio and Stone examined the relationship of altitude, and therefore radiation level, to cancer mortality and despite all the pitfalls in such studies a negative correlation was suggested. Dr. Chen (Beijing) described the study of very large populations in two areas in China in which the background radiation differs by a factor of about 3. The mortality rate for all cancers was reported to be lower in the higher background radiation area than in the control area. This finding is nectar to the proponents of hormesis. The populations were carefully matched but taking account of all factors, some of which may not even be suspected, is a testing task. As Chen said, "more information is needed."

Dr. Izumi (Nagasaki Univ.) reported on the effects on the thyroid of residents in the Nishiyama district of Nagasaki who were protected by the mountains from direct effects but exposed

to the fallout from the atomic bomb. This population was compared to survivors of the direct radiation. Thyroid nodules were found in 4.9% of the residents who were thought to be exposed to the fallout radiation and in 4.2% of those exposed directly to the atomic bomb radiation. These incidences can be compared to 1.6% in the control population. The study indicated a marked sex- and age-dependency. In those exposed to the atomic bomb radiation, there was a significant increase in the incidence of nodules in females but only in those aged less than 20 years at the time of exposure. There was no increase in the incidence in males. The estimated maximum dose to the thyroid from fallout ^{137}Cs was 0.12-0.24 Gy. The question was raised about what level of fallout had occurred with atomic bomb tests, in particular the Chinese tests, and whether this had contributed to the total dose. The answer was not known.

Dr. Shimizu (RERF) reviewed the findings of Life Span Study with Radiation Effects Research Foundation for the 1950-1985 period, based on DS86. Increases in cancer of breast, lung, esophagus, stomach, colon, ovary, bladder, thyroid and an increase in multiple myeloma were found. No excess has been detected yet in cancer of the rectum, gallbladder, pancreas, prostate, uterus or of malignant lymphoma. In the sample of 42,000 persons exposed to 0.1 Gy or greater, there has been an excess of 80 leukemias and 260 other cancers, a ratio of solid cancers to leukemia of 3.25. This ratio will continue to increase because the excess in leukemia is now very small but a majority of the atomic bomb survivors are still alive (62% in 1985). The UNSCEAR risk estimate of total cancers in 1977 was based on a prediction that the final ratio of solid cancers to leukemias would be 5:1. Those exposed when young are now reaching the age at which cancer incidence increases in the unexposed population and the excess of some solid cancers occurs only when the age at which the incidence of the same types of cancer starts to rise in the unexposed population is attained. This clearly demonstrates that initial events persist and that age-dependent host factors determine expression of the initial events. Thus, while the initial events are essential it is the host and exogenous factors that influence expression of the cancer potential.

Nomura's (Osaka Univ.) experimental work on paternal exposure and cancer in the progeny of mice preceded by quite some years Gardner *et al*'s findings at Sellafield. Nomura's findings were that irradiation of spermatogonia increased the incidence of lung tumors in the F_1 generation of ICR mice but did not increase leukemia. However, doses in the range of 0.36-5.04 Gy to spermatids and spermatozoa increased the incidence of leukemia 2-3 fold, whereas, in two other strains a 5-10 fold increase in leukemia was found in the F_1 generation after exposure of spermatogonia to 5.04 Gy of x rays.

The striking difference in the experimental results from the findings that have been considered to be mechanistically similar in humans is that the doubling dose is about 40 times greater in mouse than man.

Sasaki (NIRS, Chiba) reported the results of a study of B6C3F₁ mice irradiated at 17 days gestation, at birth, and 7, 35, 105, 240 or 365 days of age. The most sensitive age for life shortening was in the early postnatal period. The study showed that each tumor type has an individual age dependency. Fetal and neonatal mice were not sensitive to the induction of myeloid leukemia or Harderian gland tumors but the susceptibility for induction of lung, liver, and pituitary tumors, for example, was high in late fetal development. Benjamin (Colorado State Univ.) recounted the experience with the dogs irradiated at 8, 28 or 55 days postcoitus and 2, 70 and 365 days postpartum. The doses used were 0.16 and .83 Gy. Surprisingly the unexposed control dogs had no mammary or other malignant tumors but tumors, including malignancies, were found in dogs irradiated in the perinatal period. Tumors appeared within 4 years postirradiation and more frequently in females. Benjamin suggested that perhaps the fact that during embryogenesis several protooncogenes are expressed might influence radioresistance to tumor induction in the early stages of embryogenesis.

The first paper of the session on experimental carcinogenesis was by Ullrich (Univ. of Texas at Galveston). The in vivo/in vitro mammary cell system is being used to study the progressive changes in tumorigenesis. The frequency of an altered phenotype characterized by subculturability is high after irradiation. While 1.0 Gy induces 20% incidence of mammary tumors in the BALB/c mice, injections of cells isolated from mammary glands exposed to 1.0 Gy into cleared fat pads will cause neoplasms in every fat pad. Clifton and Gould (Univ. of Wisconsin) have reported similar results. These workers also found that chemical carcinogens induce fewer initially altered cells but that more go on to express the cancer potential than after irradiation. Ullrich reported that over expression of c-myc was detected in the mammary cells. An early change detected by a monoclonal antibody was a mutant of P53 which suggests the importance of suppressor genes. Although not tested for in the early cell passages, Rb mRNA expression was lost in late passages. Using an assay developed by Folkman, the angiogenic activity was assessed after exposure to gamma rays and neutrons. Angiogenic activity was found early and more frequently after neutrons than gamma irradiation.

Covelli (ENEA, CRE Casaccia) discussed dose-response relationships, especially for high-LET radiation. Quadratic and linear dose-response curves were considered the best fits to the initial slopes of the curves for myeloid leukemia and liver tumors after exposure to low- and high-LET radiation

respectively. If this is the case, RBE values must be very high at very low doses and would not show any limiting value, a finding that is different from those at ANL and ORNL. In the case of ovarian tumors no simple model fits the data and there is a threshold response. The response is consistent with the mechanism suggested many years ago, namely that the radiation, even at very low doses, kills the sensitive oocytes upsetting the ovary-pituitary hormonal feedback leading to increased and protracted gonadotrophin secretion that in turn results in tumors of the follicular cells. In the liver a very marked age dependency for susceptibility was found. The susceptibility decreased from the highest, when the fetus was irradiated, and the lowest at 9 months of age, the oldest age tested. The results suggested that RBE for liver tumor induction also decreased with age.

Seed (Argonne National Laboratory) described the stages in the development of myeloproliferative disease in beagle dogs. It is well nigh impossible to induce excess myeloid leukemia in dogs with single doses. Dogs are radio-sensitive and have a low LD_{50} and at the highest doses at which you get survival the induction rate of leukemia is low so that excess leukemia could only be determined with very large sample sizes. However, at low dose rates, 0.17 Gy/day and less, but at high total doses, >12 Gy a high incidence of myeloproliferative disease occurs. There is four-stage sequence in the development of the disease: (1) suppression (bone marrow damage); (2) recovery with compensatory increase in proliferation; (3) accommodation; and (4) preleukemic transition. An interesting characteristic is the crisis when in some animals the increasing aplastic anemia leads to death while others recover and become candidates for leukemia with a probability of about 0.5. Accompanying this recovery, and perhaps the reason it occurs, is the development of increased radioresistance of the bone marrow cells. This adaptation is reflected in the appearance of a shoulder in the cell survival curve for the granulocyte-monocyte stem cells, an increase in D_0 and in split-dose recovery. These results suggest an acquired increase in the ability to repair the radiation-induced damage. It would be interesting to know if the analogy of these preleukemia changes with the changes that occur in in vitro cell transformation as cells go through crisis and change from a cell strain to a cell line can be extended to the changes from a diploid to a aneuploid state that occurs in cells in vitro.

Unfortunately, dog chromosomes and aberrations in them are difficult to analyze. However, a nonrandom lesion has been found in chromosome 1 and the percentage of cells showing this lesion, which appears before the crisis, increases at a rate consistent with some power function. This might signify clonal expansion. Clearly at some stage after the crisis the cells acquire autocrine function and autonomy. If the irradiation is stopped before this stage, leukemia does not appear to develop.

Yokoro (Hiroshima University; Dr. Yokoro will move to Nagasaki to join RERF in 1991) and his colleagues have compared the carcinogenic effects of tritiated water with the radiation of other qualities. Tritiated water was administered by a single interperitoneal injection and if the dose was 20 mCi/mouse, or less, the mice survived long enough to get tumors in many tissues. There was a striking lack of dose dependence for tumor induction between 3.75 mCi and 15 mCi. When the mice were given 0.25 mCi/ml continuously in drinking water, the tumor incidence was 70% (0.05 mCi/ml), 77% (0.25 mCi/ml) and 83 (0.1 mCi/ml) with a preponderance of T-cell lymphomas of the thymus. In the highest concentration the ratio of T-cell lymphomas to the total tumors decreased as the concentration is lowered.

Clifton (Univ. of Wisconsin, Madison) discussed the cells of origin of radiogenic thyroid cancer. Clifton developed an in vivo-in vitro method for studying the induction of thyroid cancer some years ago in which follicular cells are dispersed and injected into fat pads where they reform into functional thyroid follicles. Transplantation assays indicate that about 1% of the monodispersed follicle cells are clonogens. Initiation of these clonogens by radiation is a common event although overt cancer is not. The expression of the initiated cells is influenced by the number of normal cells in the grafts. The more normal cells there are in the graft the lower the frequency of the development of cancers. The question is whether this suppression of the expression of the oncogenic potential is due to cell-cell interactions or a hormonal feedback. It appears that both operate and when sufficient cells are grafted the thyroid-pituitary axis can be reestablished. The conclusion was that the thyroid clonogens have all the characteristics of stem cells and must be presumed to be the cells at risk for cancer induction.

The cells at risk and the development of thymic lymphoma was discussed by Muto (NIRS Chiba). In a elegant study thymocytes from B10 Thy-1.1 mice, one month after irradiation, were sorted into four subpopulations using anti-CD4 and anti-CD8 monoclonal antibodies. When these separate cell populations were injected into the thymus, the subpopulation that gave rise to thymic lymphomas could be identified from the presence of the markers. Two other markers, the J11d and TL-2 antigens, which are not expressed in normal thymocytes, appear in the cells of animals exposed to the fractionated irradiation. The results indicated that the cells at risk for the induction of thymic lymphoma were not the undifferentiated stem cell but committed cells with proliferative capacity. Sado (Chiba), with whom Dr. Muto works, discussed the results of their experiments which are concerned with the complex interactions between cells that originate in the bone marrow and with those of the thymus. In the experiments using bone marrow transplantation, B10 Thy 1 congenic

mice were exposed to the classical 4 weekly exposures of 1.5 Gy. When the irradiated B10 mice were grafted with bone marrow cells from normal B10 donor mice, tumor development was suppressed because the transformation of the irradiated thymocytes to prelymphoma cells was suppressed. The results of a number of different experiments suggest that the radiation-induced depletion of thymocytes is followed by repopulation of the depleted thymus with T cell precursors that are more radioresistant and are part of the residual thymic cell population. The prelymphoma cells arise from the regenerating thymic cells and it appears that this involves an arrest in differentiation and a loss of growth control before they proceed to form thymic lymphomas.

Kamiya (Hiroshima Univ.) and colleagues have used the rat mammary cell transplantation system to assay epithelial clonogens. When cells are grafted into the host two types of cell colonies may form, alveolar and ductal. The cells of the ductal colonies retain clonogenic ability whereas the alveolar cells, which differentiate to produce milk, do not. Hormonal manipulation was used to influence differentiation. For example, a pituitary and an estrogen releasing tube implanted into the spleen plus adrenalectomy result in a seven-fold increase in DNA in the mammary gland and about a five-fold increase in clonogens. When such mammary glands were irradiated, carcinomas increased linearly with dose with shorter latent periods and a significantly higher cancer incidence than in rats irradiated but without the hormonal manipulation to increase the number of clonogens.

Tanooka (National Cancer Center Research Institute, Tokyo) reported some of his experiments on the carcinogenic effects of beta rays from $^{90}\text{Sr}/^{90}\text{Y}$. The resistance of the mouse skin to tumor induction is well shown by the lack of tumors after single doses up to 170 Gy. The presence of initiated cells could be demonstrated by the application of 4-nitroquinolone 1-oxide on the skin. Multiple exposures, three times a week to doses in the range of 2.5-11.8 Gy per fraction, caused 100% incidence of skin tumors and also some bone tumors. As the dose per fraction was decreased, the latent period increased and the tumor incidence decreased with only 1 squamous cell carcinoma and one osteosarcoma with lifetime exposures to 0.75 Gy per fraction. Interestingly, TPA did not promote tumors exposed to multiple doses of beta rays. It was established that the induced skin tumors were monoclonal in origin.

Radiation-induction of skin cancers was also the subject of Burns' (New York, University) talk. It has become dogma that carcinogenesis is a multistage process. If that is the case in radiation carcinogenesis, how many stages are there? Burns noted that the incidence of squamous and basal cell carcinomas is consistent with two events or a quadratic response; based on split dose experiments, there is a capability for repair.

Burns suggested that a dose-response relationship independent of elapsed time can be formulated if the tumor yield can be separated into a product of two functions; of dose and one of time and one can be expressed as $Y(D,t)=F(D)g(t)$ where $Y(D,t)$ is the cancer yield per animal, D is dose, and t is the elapsed time after exposure. The experimental data for tumors in irradiated rat skin is considered to be a power function of the rats' lifespan. The Weibull is one such power function that is consistent with the multistage theory of carcinogenesis. Based on the linear-quadratic model $F(D)=CLD + BD^2$, where L is linear energy transfer, D is dose, and C and B are constants the dose-response becomes predominantly linear as doses are increasingly lowered and as the LET is increased. It should be noted that when different tissues are compared other factors, probably target size and number, must be taken into account. There was evidence that c-myc is amplified and expressed in carcinomas but not in the one sarcoma tested. K-ras was also activated, which involves a point mutation, but the probability that this change is radiation-induced must be small. There is the question in skin, just as in the case of other tissues of what changes are primary and which are secondary.

Sadamori (Nagasaki Univ.) examined the atomic bomb survivors recorded in the Scientific Data Center of Atomic Bomb Disaster at Nagasaki University School of Medicine. One hundred and fifty cases with skin cancer were identified in the 65,268 survivors. The ratio of basal cell carcinomas to squamous cell carcinomas is about 1.6, a much lower ratio than the ratio found in other irradiated and unexposed populations. Distance from the hypocenter was used as a surrogate for absorbed dose and a significant inverse correlation between the incidence of skin cancer and the distance from the hypocenter was found. Hopefully the incidence of skin cancers as a function of dose will be determined for all the atomic bomb survivors.

The next talk by Bowden (Univ. of Arizona) concentrated on the molecular changes in the cells of radiation-induced skin cancer. In the context of the operational division of skin carcinogenesis into initiation, promotion, and progression Bowden discussed the effects of ionizing radiation. He suggested that ionizing radiation was a weak initiating agent in the production of malignant squamous carcinomas. DNA extracted from different types of tumors initiated by x rays and promoted with TPA shows dominant transforming activity. Unlike chemical carcinogenesis of the skin, the ras family is not involved. In squamous cell carcinomas three different transforming genes were identified. The question is whether any of these changes are due to direct action of the radiation. Radiation-induced progression was studied using a line of cells capable of forming papillomas. Irradiation of the benign cell line induced a malignant cell that showed high levels of

transcripts of c-fos, c-jun and stromelysin which degrades the basement membrane, transin and metallothionein II A genes. The increased level of stromelysin is related to the action of the stromelysin promoter. These studies suggest that by astute development of cell systems it should be possible to unravel the molecular changes in the carcinogenic process.

Niwa's (Hiroshima Univ.) study was about the oncogene changes in radiation-induced thymic lymphomas. In these tumors c-myc was expressed at a high level but the gene showed no rearrangement. However, a loss of certain loci was found using a mini satellite probe. Terada (National Cancer Center Research Institute) was concerned with the attribution of the various genetic alterations. The genes in which changes occur differ in different types of human cancer although some changes are common to some types of cancer. It is becoming clear that loss of heterozygosity at a number of loci is a common feature of human cancers, for example, P53 and Rb genes and the remaining alleles show mutations and thus a loss of the normal gene products of these suppressor genes. It is probably reasonable to believe that the number of suppressor genes that will be identified will increase. The importance of the sequence of the changes in suppressor genes and oncogenes is recognized but the sequence is not known.

Kamada (Hiroshima Univ.) presented results obtained from the cytogenetic examination of 75 radiation-related leukemias. Molecular studies have not revealed association with point mutations of N and K ras genes or in rearrangements of the ber gene and the leukemias.

Sasaki's (Kyoto Univ.) talk dealt with tumor suppressor genes and, in particular, the question of paternal imprinting. The latter possibility stems from the observation that in sporadic nonfamilial osteosarcoma and the osteosarcomas after radiotherapy that most of the initial somatic mutations were assigned on the copy of the Rb gene derived from the father. It is hoped that the work will reveal the mechanisms of the bias toward the paternal origin in the germinal and somatic mutation of tumor suppressor genes.

Nettesheim (NIEHS) discussed the role of the growth factors, TGFs α and β , in the regulation of proliferation of normal and transformed rat tracheal epithelial cells. TGF α is a polypeptide that is structurally related to epidermal growth factor (EGF) and binds to the EGF receptor. TGF α is also secreted, but in small quantities, by normal tracheal epithelial cells. It appears that neoplastically transformed epithelial cells become less dependent on such factors as insulin, EGF and pituitary extracts and that growth is influenced by the autocrine TGF α . This change in the factors controlling cell proliferation is a fairly early change. TGF β , which is secreted in a latent form and must be activated, plays a different role and is important in the cell-cell

interactions that are important in controlling cell population.

On December 7, the day began with a visit to a small number of the laboratories at the National Cancer Center Research Institute after a brief but amusing session with Dr. Sigimura. Then it was on to the National Institute of Radiological Sciences at Chiba. Dr. T. Sado had invited me to recount the aims, design, findings and failures of the radiation late effects studies at Argonne and Oak Ridge National Laboratories. The group at Chiba is considering what long term animal studies they should undertake.

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APPENDIX

Itinerary

- Dec. 2-3 Travel from Oak Ridge, Tennessee to Tokyo, Japan
- Dec. 4-6 Attend and present an invited paper at the International Symposium on Radiation Carcinogenesis in the Whole Body System.
- December 7 Present an invited lecture on radiation studies at the National Institute of Radiological Studies
- December 8 Travel from Tokyo, Japan to Oak Ridge, Tennessee

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