4. Research Center for Radiation Emergency Medicine

Kenzo Fujimoto, Ph.D.
Supervisory Director

Outline of Research Career:

Dr. Fujimoto graduated in Science from Kyoto University and obtained a Doctoral Degree in Engineering at the University of Tokyo. He has spent most of his career in studies on natural environmental radiation, especially terrestrial gamma radiation and indoor radon. After the criticality accident at JCO in Tokai his major involvement shifted to dose estimation for radiation emergencies. He was at the Harvard School of Public Health as a visiting scientist from 1981 to 1982 and in the International Atomic Energy Agency as an environment protection specialist from 1990 to 1994. He also served as a lecturer at the University of Tokyo from 1989 to 1996. He is now Director of Research Center for Radiation Emergency Medicine (since 2003), an International Editorial Adviser of the *Journal of Radiological Protection* and an Advisory Editorial Board Member of *Nuclear Technology & Radiation Protection*.

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Objectives:

This Research Center had the unique experience of receiving three highly exposed victims at the time of the JCO criticality accident in Tokai in September 1999, because the Center has been assigned as the final stage radiation emergency medicine hospital within the nuclear disaster prevention plan of the Japanese government since 1980. The Center is responsible for, and has established a solid system for dealing with a radiation emergency.

Our required aims are as follows.

To accept radiation exposed victims who require specialized diagnosis and treatment

To dispatch a radiation emergency medical team to local emergency medical headquarters

To facilitate exchange of information, research activities, and human resources, by constructing networks in cooperation with other organizations who could deal with a radiation emergency

To maintain and reinforce an efficient radiation emergency medicine system under normal conditions

To promote technical development and research on radiation emergency medicine

To develop skilled manpower for a radiation emergency

Other objectives are research on radiation emergency medicine to be carried out as a project involving scientists not only in this Research Center but also the Research Center for Radiation Safety. Details are given elsewhere; only subjects are given here.

1. Studying pathologic physiology of high-dose exposure
2. Developing chelating agents for removing radionuclides
3. Developing systems for precise measurement and evaluation in emergencies
4. Mitigating radiation injuries
5. Developing emergency responses to environmental contamination

Overview:

After the nuclear accident at Three Mile Island in 1979, the Central Disaster Prevention Council (CDPC) in the Prime Minister's office reinforced emergency preparedness for dealing with a nuclear power station emergency and issued a report "Urgent Disaster Countermeasures to be taken for Nuclear Facilities by Governmental Agencies" in July, 1979. In June 1980, the Nuclear Safety Commission (NSC) came up with a guideline entitled "Off-site Emergency Planning and Preparedness for Nuclear Power Plants." This guideline nominated NIRS as a tertiary radiation emergency hospital that serves as the final stage hospital for receiving heavily exposed or contaminated victims due to nuclear or radiological accidents. From January 2004 the Research Center has served as a liaison institution of WHO/REMPAN.

The Research Center carries out the following activities to maintain and enhance or strengthen the emergency preparedness system required to fulfill its role as the tertiary radiation emergency hospital.

1) Network System

The primary goal is strengthening its institutional system to prepare for radiation emergencies by establishing three nation-wide network councils, for

medicine, chromosome analysis as bio-dosimetry, and physical dosimetry.

1-1. NIRS Radiation Emergency Medicine Network Council

This is a group of experts and medical organizations from which NIRS asks for help to treat the victims at the time of a nuclear disaster or a radiological accident. The cooperation involves dispatch of an expert in the specific field in an emergency, arrangement of acceptance of patients at medical facilities affiliated with the expert's organization, and provision of advice. Such collaboration is expected to reinforce the functions of NIRS. NIRS will call the Radiation Emergency Medicine Network Council to solicit cooperation when it is requested by authorities (or when NIRS thinks the necessity arises) to respond to radiation emergencies. This council was working effectively at the time of the JCO criticality accident in 1999.

1-2. Chromosome Network Council

This council forms a network among a limited number of specialists having dose evaluation capability based on chromosome analysis. Through this network, NIRS can strengthen the capability of the dose estimation by chromosome aberration, and also enhance the technical standards of chromosome aberration dose estimation method.

1-3. Physical Dosimetry Network Council

This council is a network of experts in physical dose evaluation techniques. The network is expected to respond to emergencies through collaboration among experts for prompt and precise dose estimation. It is also responsible for accumulating dose evaluation technology and for fostering followers.

1-4. Local Medicine Network Council

In Japan, medical systems are currently being constructed in accordance with disaster prevention plans of local governments that have nuclear facilities in their territories. Within the framework of each local nuclear disaster prevention plan, set up of a specific collaboration system with NIRS is mandatory and it must specify the steps to be performed in the prompt transfer of patients from a site to a hospital, including radiation protection management at the hospital.

2) Training

The primary goal is the development of radiation emergency medicine skills for medical professionals and disaster prevention personnel; these include doctors and nurses involved in nuclear disaster medical care, emergency crews, and nuclear establishment employees. For that purpose the following training courses are regularly held in addition to our participation in nuclear disaster prevention training, seminars on medical response and other activities conducted by local governments to disseminate the relevant information and skills to deal with a radiation emergency.

(A) Radiation emergency medicine course
The course is held three times a year with 20 participants in each course. More than 260 participants have been trained so far. Many of them are working actively in primary or secondary medical emergency hospitals and playing an important role in local radiation emergency exercises.

(B) Emergency rescue training course
The course is held three times a year with 30 participants in each course. The duration of the course was one week.

(C) Training course for the “whole body counter” measurement
The persons who are responsible for estimation of internal exposure dose in the case of a radiation emergency were trained to be able to measure and estimate internal dose by themselves.

3) Emergency Exercises

Japanese national and local governments regularly organize emergency exercises to which we send our staff to take roles in emergency medicine and radiation protection. On 10 November 2005 the Japanese government conducted a nuclear disaster prevention exercise in Niigata prefecture. Our staff participated in this. Moreover we conducted an additional exercise to simulate emergency handling of a patient transferred to NIRS by helicopter (Fig.7).

4) Follow-up Studies

The Research Center for Radiation Emergency Medicine conducts research work in a wide range of areas: medical care, radiation measurement and investigation, health physics, cytogenetics, and psychology. In addition, we study dose evaluation which facilitates decision-making in treatment methods, identification of radionuclides, treatment for high-dose exposure or reduction of high-dose exposure hazards, and rapid evaluation of population exposure.

The center also carries on follow-up clinics for the victims of the thermonuclear weapons test on Bikini Atoll, patients with thorotrastosis and the surviving JCO accident victim.

4-1. Follow-up examination of the victims of the Bikini nuclear test

During the nuclear test on Bikini Atoll on 1 March, 1954, 23 crew members (18 to 39 years old

at the time) of the Dai-go Fukuryu-maru out of Yaizu City, Shizuoka Prefecture, were exposed to radiation. This follow-up survey aims to examine the physical states of these patients over a long period of time to study late radiation injuries. The follow-up examinations that have been conducted for 50 years provide precious data. The mode of exposure was composite, and the estimated dose was 1.7 to 6.0 Gy. A physical checkup of still living survivors was conducted at Yaizu City General Hospital this year.

4-2. Follow-up examination of patients with thorotrastosis

Thorotrast is a radioactive contrast medium for angiography. The main constituent is thorium dioxide. A German company started sales of this medium in 1930. In Japan, the product was used from 1932 to 1945 for 10,000 to 20,000 patients, the majority of whom were killed in World War II. Thorotrast is deposited in the liver and spleen and causes internal radiation exposure over a long period of time. This follow-up examination estimates the amount of thorium deposited in surviving patients, investigates their clinical symptoms, analyzes the relationship between the deposited amount and malignant carcinogenesis, and elucidates the effects of long-term internal radiation exposure on human bodies.

5) Database

A database including the cases of radiation exposure on Bikini Atoll and cases of thorotrastosis is being constructed. Since radiation accidents are rare, the maximum amount of information must be collected from each accident and accumulated to help medical professionals decide strategies to treat patients, and establish and improve therapeutic methods. Today, there are various databases on radiation accidents and their victims, but most are not accessible from other countries. Under the supervision of the World Health Organization (WHO), an international program called REMPAN (Radiation Emergency Medical Preparedness And Response) exchanges information on radiation accidents, including those in the database owned by the US REAC/TS (Radiation Emergency Assistance Center/Training Site). REMPAN has a collaborating center at Ulm University in Germany and manages a SEARCH database of patient information. It aims to construct an international database by registering cases that are attributable to the Chernobyl accident and other radiation accidents. The NIRS registered the Dai-go Fukuryu-maru accident in the SEARCH database. In addition, our center is constructing a database by collecting the medical data of the victims of radiation accidents and exchanging information with countries that have developed radiation accident medicine.

6) International Cooperation (Fig.8)

(A) Our center participated in CONVEX (3) Exercise organized by WHO on 11 and 12 May 2005.

(B) Three professionals from Beijing Institute of Radiation Medicine and five from Taiwan visited our facility and discussed radiation emergency medicine with NIRS staff.

(C) Our staff was invited to deliver lectures in the following meetings and training courses.

(1) A training course held in Thailand from 5 to 11 June 2005.

(2) 2005 Radiation Emergency Medical Care Workshop held in Taipei on 29 and 30 July.

(3) European Bone Marrow Transplantation Radiation Accident Consensus Meeting held in Vaux de Cernay in France on 25 and 26 October 2005.

(4) Workshop on Research and Training Advancement in Radiation Emergency Medicine held in Seoul on 3 and 4 November 2005.

(5) Third National Convention on Health Emergency Management held in Manila from 4 to 7 December 2005.

(D) A training course on Medical Treatment of Patients Contaminated with Alpha Emitters was held for 15 medical doctors from Tri-service General Hospital in Taiwan on 1 and 2 September 2005.

(E) Our staff attended International Conference on Monitoring, Assessments and Uncertainties for Nuclear and Radiological emergency Response held in Rio de Janeiro from 21 to 25 November 2005.

(F) Our staff was invited to attend DOE/IAEA Assistance Work Group (AWG) and Expert Groups (EG) meetings held in Alexander, Ireland on 19-23 September 2005 and in Buenos Aires on 21-23 February 2006.

(G) WHO-REMPAN Regional Workshop on Radiation Emergency Medical Preparedness and Response in the Western Pacific Asia was organized on 23 and 24 March 2006 in collaboration with WHO and a regional assistance scheme was discussed with 13 participants from Korea, China and the Philippines.

(H) Our staff attended The 11th Coordination and Planning Meeting of the WHO REMPAN Collaborating Centers and Liaison Institutions

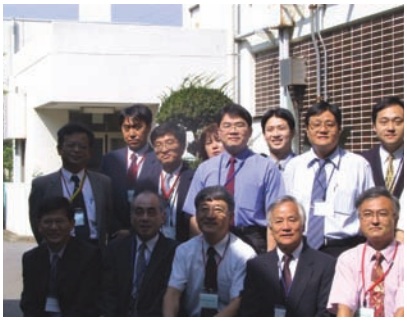
held in Kiev on 25-28 April 2006.

Receiving a patient at the heliport in NIRS

Treatment of a patient in NIRS

Fig 7. Nuclear disaster prevention exercise (10 November 2005)

Discussion with
Beijing Institute of Radiation Medicine
(26-27 April 2005)



Seminar for Tri-service General Hospital in Taiwan
(1-2 September 2005)

Fig 8. International cooperation

4.1. The Study for Radiation Emergency Medical Preparedness

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Director, Department of
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Outline of Research Career:

Dr. Akashi started his medical career at Jichi Medical School (Tochigi Prefecture) as a junior resident of internal medicine in 1981. He worked as a senior resident at the Division of Hematology of Jichi Medical School and moved to the division of Hematology/Oncology at UCLA School of Medicine in 1987. He received a Ph. D. from Jichi Medical School in 1988. He became a staff member of NIRS in 1990. His major works are:
1) establishment of radiation emergency medical preparedness; 2) research on radiation injuries, including molecular and cellular mechanisms; 3) development of methods for mitigation of radiation injuries. He has treated patients of the criticality accident in Tokai-mura.

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Objectives:

1) Study on patho-physiology in exposure to high-dose radiation

This study aims to understand the effects of high-dose radiation on intracellular signal transduction and the mechanisms of transmitting the signals among cells; these need to be known for treatment of acute radiation injury. The study also aims to identify genes that are related to skin injury caused by high-dose radiation, and to establish an in vitro model system of gene therapy for radiation injuries to skin.

2) Study on agents for removing radionuclides that have been incorporated

The study does experiments using experimental animals to investigate the removal of radionuclides (RNs) that have been incorporated by new agents and also to examine their adverse effects. This study aims to prepare manuals describing safe and effective treatments with these agents (DTPA, Prussian blue, etc.) for accidents of internal contamination on the basis of the data from these experiments.

3) Establishment of systems for radiation measurement and dose-assessment in emergencies

This research aims to develop devices for measuring low-level radiation in easy-to-prepare specimens by fast and precise methods for evaluating the dose received. This study also includes development of methods for biological dose estimation.

4) Rsearch on the mitigation of radiation injuries

This research investigates factors or agents to mitigate the damage to patients exposed to radiation by conducting animal experiments. The study also aims to quantify the effects of protectors on late radiation effects using mice that have gene mutation markers.

5) Study on emergency response to environmental pollution with RNs

Aims of this study are to prepare for environmental pollution due to accidents at nuclear facilities, mishandling of RNs at research institutions, missing radiation sources, or accidents during transport of RIs. It focuses on the development of new technology for identification of contaminated areas and estimation of doses received by rescue teams and residents at an accident site. Development of various accident scenarios and handling manuals is also envisaged.

Progress of Research:

1) Study on patho-physiology in exposure to high-dose radiation

Roles of reactive oxygen species (ROS) in damage to mitochondrial DNA (mtDNA) following ultraviolet (UV)-irradiation were investigated in the human hepatoma cell line SK-HEP-1. We altered the intracellular status of ROS by the overexpression of manganese superoxide dismutase (MnSOD) and/or catalase. Using HPLC, we analyzed 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodGuo), known as a marker of damage to DNA molecules. UV-irradiation resulted in the accumulation of 8-oxodGuo in these cells. The overexpression of MnSOD enhanced the accumulation of 8-oxodGuo by UV. The co-overexpression of catalase inhibited the accumulation of 8-oxodGuo by UV in MnSOD-transfectants. The overexpression of MnSOD reduced the colony forming capacity in SK-HEP-1 cells and the co-overexpression of catalase with MnSOD stimulated the capacity compared to control. UV-irradiation inhibited the colony forming capacity in these cells; no difference was observed among the capacities of control, MnSOD- and catalase-transfectants. However, the overexpression of MnSOD/catalase significantly rescued the reduction of colony forming capacity by UV-irradiation. Our results suggest that the accumulation of hydrogen peroxide plays a key role in the oxidative damage to mtDNA of UV-irradiated cells, and also that the overexpression of both MnSOD and catalase reduces the mtDNA damage and blocks the growth inhibition by UV. Our results also indicate that the increased activity of MnSOD may lead to a toxic effect on mtDNA by UV-irradiation.

2) Study on agents for removing radionuclides that have been incorporated

Recently, many reports have demonstrated that chemical structure of uranium varies according to pH of the dissolved solution, suggesting that the toxicity may be altered *in vivo* and the effects of chelating agents may also be affected. In order to clarify effects of pH on the toxicity of depleted uranium (DU), five groups of male rats (each group consisted of five rats), were injected intramuscularly with 8 mg/kg DU dissolved in solution adjusted to pH 1, 3, 5, 7 and 10. Rats were observed for 21 days. Within 6-10 days after DU injection, three rats died in the pH 3, 7 and 10 groups, indicating the survival rates were related to pH; the survival rate was the lowest (40%) in the pH 10 group. The ratio of NAG/creatinine, which is a biochemical marker of renal function and the total DU concentrations in the kidney, liver, spleen, femur increased in a pH-dependent manner; DU was the highest in the pH 7 and 10 groups. The levels of DU in the muscle injected site also increased in a pH-dependent manner, and were the highest in the pH 5 and 7 groups, indicating that the formed uranium was not removed easily or excreted from the body. The results demonstrate that DU toxicity depends on pH.

We also examined the effects of pH on DU removal by chelating agents. Five groups of male rats (each group had 15 rats) were injected intraperitonelly with 8 mg/kg DU dissolved in the solution with either pH 1, 3, 7 or 10. In each pH group, then, five rats were injected intraperitoneally with a chelating agent, either 240 mg/kg CBMIDA [catechol-3,6-bis(methyleiminodiacetic acid)] or 10 mg/kg EHBP (ethane-1-hydroxy-1,1-bisphoshonate) continuous by for 3 days; the remaining five rats were used as control with no chelating agent. At pH 7 when various DU-complexes were formed, the DU toxicity, including renal dysfunction, increased, and preventing DU-induced toxicity. The efficacy of CBMIDA was superior to EHBP, particularly in the prevention of renal dysfunction. The results demonstrated that the removal effects of chelating agents varies according to pH differences, and lost completely at pH 7, indicating that the treatment with chelating agent should begin in the DU-contaminated person as soon as possible after an accident.

Effects of Deperiprone, a medicine for Thalassaemia and five newly synthesized compounds for removal of incorporated DU were tested in rats. Among them, Deperiprone and 4,6-demethyl-1-hydroxypyrimidin-2 (1H)-one were effective for decreasing DU deposition in the injected muscle, excreting DU in urine on the first day, and preventing renal damage. However, no significant increase in the amount of DU in the excreta or decrease in DU concentration in organs other than the muscle was found. The results are inconclusive, and therefore further studies are required. .

3) Establishment of systems for radiation measurement and dose-assessment in emergencies

For treatment of internal contamination, detection of radionuclides at an early stage plays an important role in radiation emergency medicine. Especially for making treatment decisions, identification of internally incorporated RNs is essential. A quick detection system which can identify RNs taken in the body was developed. The system was designed for the measurement of α-, β-, and γ-rays by four π-coincidence method, which consisted of two detectors and a signal processing unit. These detectors were NaI(Tl) and liquid scintillators. The

NaI(Tl) scintillator (well type of 40mm diameter) was used as a γ-ray detector and also as a guard counter for the liquid scintillator. The liquid scintillator, with which the subject specimen was intermingled homogeneously was put in a polypropylene vial and placed in the well of the NaI(Tl) scintillator. Scintillation light generated by β or α-rays in the liquid scintillator was distributed optically onto two photomultipliers through a half mirror. Only the signals from these photomultipliers which had simultaneity were summed again in order to reduce random thermal noise generated in each photomultiplier. Detector signals from the NaI(Tl) and liquid scintillator were digitized directly at the front-end of the signal processing unit with 14-bit ADC. The data were also processed in FPGA (Field Programmable Gate Array) and FIFO (First In First Out) memory for waveform capture. These energy and signal pulse shape data with time stamps of each event were employed in the DSP (Digital Signal Processor) of a subsequent stage. β-rays were then distinguished from α-ray in the DSP by the difference of signal decay pattern. Consequently, the time correlation with γ-rays and these identified α or β-rays were examined in a computer to determine the RN. Evaluation of spiked sample with ^{241}Am demonstrated sensitivity down to 0.1 Bq/cm^3 with 30 minute measurement.

4) Research on the mitigation of radiation injuries

Radioprotective effect of TMG (2-(α-D-glucopyranosyl)methyl-2,5,7,8-tetramethy- chroman-6-ol, a water-soluble vitamin E derivative) and selenomethionine containing torolox derivative (TroSeM) was studied in mice following whole-body X-ray irradiation. These compounds show excellent antioxidant activity with strong superoxide and hydroxyl radical scavenging ability in examination using a spin-trapping method employing ESR *in vitro*. A solution of TMG (dissolved in saline) or TroSeM (suspended in 0.5% methylcellurose) was administered intraperitoneally to C3H mice (male, 10 weeks old) before or after whole-body X-ray irradiation, and the protection for TMG and TroSeM against lethal irradiation was evaluated from 30-day mouse survival rate, TMG (650 mg/Kg) was injected ip just before or after the X-ray irradiation(7 Gy), the survival rate was about 80% showing a significantly high survival rate compared to the control experiment (25%). The survival rate was 50% even when administrated 60 min after irradiation. The $LD_{30/50}$ was about 7.8 Gy for TMG-injected mice (administrated immediately after irradiation) and 6.6 Gy for control mice, yielding a DRF for TMG (650 mg/kg bw) of 1.18. On the other hand, TroSeM (30mg/Kg) was injected ip 30 min before X-ray irradiation (7.5 Gy), the survival rate was about 60%, whereas it was about 40% immediately after irradiation in contrast to control (10%). TroSeM was effective both pre- and post irradiation against lethal irradiation. Since most of the radioprotectors were effective when administered prior to irradiation, the effectiveness of these compounds when administered postirradiation suggests possibility for protection against accidental radiation exposures.

5) Study on emergency response to environmental pollution with RNs

In the case of radiological emergency due to missing sources or contamination, it is necessary to find out the location of the sources. For that purpose one of the simplest γ-spectrometry systems that can provide directional information of incident γ-rays has been developed. The system consists of a 3" x3" ϕ NaI (Tl) scintillator, a specially shaped lead shield, and software. The measurement was carried out four times by rotating the shield position along the axis of the detector to obtain four energy spectra at one location. Four count rates at a special region of interest in the spectra were fed into the software for determining incident directions of γ-rays. Experiments using ^{137}Cs and ^{54}Mn at the same time demonstrated that the direction of γ-rays from several dominant sources from any direction could be identified with good precision in a total measurement time of 10 to 20 minutes. The system could be used to identify the locations of missing radioactive sources or the cause of elevation in ambient radiation dose rates. The disadvantages of the present system are follows. (1) It requires four time measurements at one location. (2) It can provide only one pseudo incident angle when several contamination sources exist around the detector system and emit the same energy γ- rays. (3) It can scan only one plane geometry which is usually chosen as the horizontal plane.

Major publications:

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2) Saori Kawamura, Daisaku Takai, Keiko Watanabe, Makoto Akashi, et al. Role of Mitochondrial DNA in Cells Exposed to Irradiation : Generation of Reactive Oxygen Species (ROS) is Required for G2 Checkpoint upon Irradiation, *Journal of Health Science*, **51**(3), 385-393, 2005.
3) Takuya Iyoda, Kisaburo Nagata, Makoto Akashi, Yoshiro Kobayashi: Neutrophils accelerate macrophage-mediated digestion of apoptotic cells in vivo as well as in vitro., *Journal of Immunology*, **175**(6), 3475-3483, 2005.
4) Mamoru Haratake, Masahiro Ono, Makoto Akashi, Morio Nakayama, et.al: Synthesis of hydrophilic macroporous chelating polymers and their versatility in the preconcentration of metals in seawater samples, *Analytica Chimica Acta*, **561**, 183-190, 2006.
5) Satoshi Fukuda, Haruzo Iida, Mizuyo Ikeda, Xueming Yan, Yuyuan Xie : Toxicity of uranium and the removal effects of CBMIDA and EHBP in simulated wounds of rats. *Health Phys*, **89**,81-88, 2005.
6) Satoshi Fukuda : (Review) Chelating agents used for plutonium and uranium removal in radiation emergency medicine. *Current Medical Chemistry*, **12**, 2765-2770, 2005.
7) Satoshi Fukuda, Mizuyo Ikeda, Momoko Chiba, Kazunari Kaneko : Clinical diagnostic of renal and bone damage in rats intramuscularly injected with depleted uranium. *Radiation Protection Dosimetry*, 2006, On line.
8) Kenzo Fujimoto: A simple gamma ray direction finder. *Health Physics*, **91**(1),29-35, 2006.