4. Research Center for Radiation Emergency Medicine

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 for 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 is now an Internal Editorial Adviser of the Journal of Radiological Protection and an Advisory Editorial Board Member of Nuclear Technology & Radiation Protection.

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Objectives:
The statutory function of the Research Center for Radiation Emergency Medicine is the establishment of a solid system for dealing with a radiation emergency; the Research Center is assigned as a tertiary emergency medicine hospital within the nuclear disaster prevention plan in Japan. Required aims are as follows.
1. To accept exposed victims who require further expert diagnosis and treatment
2. To dispatch a radiation emergency medical team to the local emergency medical headquarters
3. To facilitate exchange of information, research activities, and human resources, by constructing networks in cooperation with outside expert organizations
4. To maintain and reinforce an efficient radiation emergency medicine system under normal conditions
5. To promote technical development and research on radiation emergency medicine

Other objectives are research on radiation emergency medicine that is carried out as project research involving scientists not only in this Research Center but also the Research Center for Radiation Safety. Details are given in other pages; only subjects are given here.
1. Pathologic physiology of high-dose exposure
2. Chelating agents for removing radionuclides
3. Development of systems for precise measurement and evaluation in emergencies
4. Mitigation of radiation injuries
5. Emergency response 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 the emergency preparedness for 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 our 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 as the tertiary radiation emergency hospital.

A. Network System
Strengthening its institutional system to prepare for radiation emergencies by establishing three nationwide network committees, for medicine, chromosome analysis as bio-dosimetry, and physical dosimetry.

A-1. NIRS Radiation Emergency Medicine Network Council
This is a group of experts and medical organizations from which NIRS asks for their help 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.

A-2. Chromosome Network Council

This council forms a network among nationwide organizations having dose evaluation functions based on chromosome analysis under the leadership of NIRS. Through this network, NIRS can be prepared for radiation emergencies, and also help maintain and enhance the technical standards of organizations involved by providing support and advice.

A-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 in prompt and precise dose measurement systems. It is also responsible for accumulating dose evaluation technology, while fostering followers.

A-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, a specific collaboration system with NIRS is required to be set up, specifying the steps to be performed in the prompt transfer of patients from a site to a hospital, including radiation management and prevention at the hospital, and sending patients to other facilities when necessary.

B. Training

Conducting educational training in radiation emergency medicine for medical professionals and disaster prevention personnel such as doctors and nurses involved in nuclear disaster medical care, emergency crews, and nuclear establishment employees. IAEA/RCA training workshops were conducted at NIRS on radiation emergency for medical doctors in 2001 and 2004. The following training courses were held in Fiscal Year of 2003.

(1) Radiation emergency medicine course

The course was held three times in 2003 with 20 participants in each course. More than 200 participants were trained so far. Many of them are working actively in primary or secondary medical emergency hospitals.

(2) Emergency rescue training course

The course was held three times in 2003 with 30 participants in each course.

(3) Refresher seminar for emergency medicine

This was held in Sendai on August 22, 2003.

C. Emergency Exercises

Participation in nuclear disaster prevention training, seminars on exposure medicine, and other activities conducted by local governments so as to enlighten the people by disseminating radiation exposure medicine to the area.

D. Follow-up Studies

In addition to the activities required for the tertiary emergency hospital, Research Center for Radiation Emergency Medicine also conducts research work in a wide range of areas: medical care, radiation measurement and investigation, health physics, cyto genetics, and psychology. In addition, the center's researchers 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. NIRS carries on follow-up clinics for the victims of a thermonuclear explosion test on the Bikini Atoll, patients with thorotrastosis and a JCO accident victim who survives.

D-1. Follow-up examination of the victims of the Bikini nuclear tests

During the nuclear test on Bikini Atoll on March 1, 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 almost 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.

D-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 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 aims to estimate the amount of thorium deposit in surviving patients, investigate their clinical symptoms, analyze the relationship between the deposited amount and malignant carcinogenesis, and understand the effects of long-term internal radiation exposure on human bodies. Physical examinations of the patients were done in this year.
E. Database

A database contributing to exposure treatment and investigation of the victims 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 workers decide strategies to treat patients, and improve and establish 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 these accidents and exchanging information with countries that have developed radiation accident medicine. In 2003, 50 data sets for acute exposure patients were obtained from the Institute of Biophysics in Russia.
4.1. The Study for Radiation Emergency Medical Preparedness

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Outline of Research:
Recently, uses of ionizing radiation and radioactive materials are increasing at hospitals, factories, universities/institutes and others. There are also many plans for new nuclear power plants. Thus, the risk of radiation accidents has been increasing, although they rarely occur. Therefore, preparedness of organizations for radiation emergency is demanded by society. In this project, fundamental research required for diagnosis and treatment for victims is performed in various fields, such as biology, biochemistry and molecular biology, medicine, zoology, nuclear engineering, mechanical engineering, physics, and radiology.

Objectives:

1) Study on pathologic physiology of high-dose exposure.
This study team aims to understand the effects of high-dose radiation exposure on intracellular signal transmission and the mechanisms of transducing the signals among cells, which need to be known for treatment of acute radiation injury. The team also aims to identify genes that are related to skin injury caused by high-dose radiation exposure, and 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 team is performing experiments using experimental animals to investigate the removal of radionuclides that have been incorporated by new agents and also their adverse effects. This team also aims to prepare manuals describing safe and effective treatments with these agents (DTPA, Prussian blue, etc.) for use in radionuclide-contamination accidents on the basis of the data from these experiments.

3) Development of systems for precise measurement and dose-assessment in emergencies
This research team aims to develop devices for measuring low-level radiation in easy-to-prepare specimens by fast and precise methods for evaluating the dose received.

4) Research on the mitigation of radiation injuries
This research team investigates pharmaceutical products (protectors) for mitigating the damage to patients exposed to radiation by conducting animal experiments. The team 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

Fig.16. The study for radiation emergency medical preparedness
polution with radionuclides
Aims of this study are to prepare for environmental pollution emergencies due to accidents of nuclear facilities, mishandling of radioisotopes (Rs) at research institutions, missing radiation sources, or accidents during transport of Rs. 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 pathologic physiology of high-dose exposure.
Irradiation causes DNA damage and induces neoplastic transformation. In response to irradiation, cells induce genes or activate proteins that protect themselves from the external insult. Nuclear factor \( \kappa \) B (NF \( \kappa \) B) activates transcription of target genes and plays important roles in inflammation. We studied the mechanism(s) for activation of NF \( \kappa \) B by irradiation in human mononuclear cells THP-1. Gel mobility shift assays showed that irradiation stimulated the NF \( \kappa \) B-DNA binding activity of nuclear extracts from these cells. Western blot analysis using polyclonal antibody against phosphorylated I\( \kappa \) B protein showed that irradiation increased the levels of phosphorylated I\( \kappa \) B. The production of tumor necrosis factor \( \alpha \) (TNF \( \alpha \)) was stimulated by irradiation in these cells. Treatment with exogenously-added TNF \( \alpha \) also stimulated the NF \( \kappa \) B binding activity with concomitant degradation of I\( \kappa \) B. Further study found that the activation of NF \( \kappa \) B by irradiation was inhibited by a neutralizing anti TNF \( \alpha \) antibody. Macrophages from TNF \( \alpha \)-deficient mice were also defective in the irradiation-induced activation of NF \( \kappa \) B. These results indicate that endogenous production of TNF \( \alpha \) in macrophages/monocytes is required for NF \( \kappa \) B activation by irradiation. Our data also suggest that TNF \( \alpha \) in macrophages/macrophages exposed to irradiation is involved in signal transduction network initiation.

Mitochondria have their own genome encoding subunits of the electron transport chain. The recent progressive studies of mitochondria has allowed us to use mitochondria DNA(mtDNA)-depleted cells (\( \rho' \) cells) and their control cells(\( \rho^+ \) cells). Using \( \rho' \) cells, we studied the role of mtDNA in irradiation. Loss of mtDNA inhibited cell growth and reduced the level of reactive oxygen species (ROS) as compared to \( \rho^+ \) cells. \( \rho' \) cells were more resistant to irradiation than \( \rho^+ \) cells. Scavenging ROS with N-acetyl cysteine (NAC) reduced the ability of colony formation in irradiated \( \rho^+ \) cells but not in irradiated P0 cells. Upon irradiation, \( \rho^+ \) cells showed delayed G2 arrest and decreased ability of a cell to recover from the G2 checkpoint compared to \( \gamma' \) cells. Irradiation increased the generation of ROS even more in \( \gamma' \) cells. Irradiation markedly increased the levels of phosphorylated forms of ERK1/2 in \( \gamma' \) cells, whereas phosphorylated levels of the kinases were affected slightly in \( \gamma^+ \) cells. Furthermore, inhibition of the ERK pathway led to a delayed G2 arrest and a delayed recovery from the arrest in irradiated \( \gamma' \) cells, and treatment with NAC also induced dysfunction of the G2 checkpoint in irradiated \( \gamma' \) cells. These results suggest that the accumulation of ROS potentiated ERK1/2 kinases after irradiation in \( \gamma' \) cells, leading to less sensitivity to irradiation. Thus, mtDNA is important for the generation of ROS that act as second messenger.

2) Study on agents for removing radionuclides that have been incorporated
The effects of three chelating agents, CBMIDA, 3, 4, 3-LIHOPO, and Ca-DTPA, for removing Pu-239 in rats were compared. Forty female Wistar rats, 2 months old, were pre-injected intraperitoneally with 37,000Bq/kg of plutonium nitrate and divided into four groups. Thereafter the rats of three groups were injected intraperitoneally with three chelating agents at a dose of 30mmol/kg, equivalent to a daily recommended human dose of Ca-DTPA, at intervals of 24hr for 3 days, beginning 30 min after plutonium injection on the first day of treatment. Urine and feces were collected every 24 hr. On day 4, the rats were sacrificed to obtain organs including the liver, kidney, and spleen, as well as the femur and serum. The amounts of excreted plutonium in urine of the CBMIDA and Ca-DTPA groups were increased significantly over that in the 3,4,3-LIHOPO and control groups, while those in the feces of the 3,4,3-LIHOPO group were increased significantly over the other groups on the first day. The total amount of excreted plutonium by 3 day-treatments was highest in the 3,4,3-LIHOPO group. The toxicity of each agent was discussed. It is concluded that at the same doses, the effect of 3, 4, 3-LIHOPO was superior to CBMIDA and Ca-DTPA for removing plutonium in rats.

3) Development of systems for precise measurement and dose-assessment in emergencies
We studied and developed a chromosome analysis for dose assessment on a partial body exposure...
using hair root cells. Collection of hair root cells after wetting the skin had a high rate (hundreds of cells / hair root on the back of the hand). These cells were cultured and the optimal specimen was able to be made by the PCC induction and the air-dry method.

In another study, we found that the simultaneous measurement of a liquid scintillation detection machine and a germanium-detection machine was effective for detection of alpha nuclides.

4) Research on the mitigation of radiation injuries

Green tea is a rich source of polyphenols, and (-)-epigallocatechin-3-gallate (EGCG) is a major constituent of green tea polyphenols. In the present study, we investigated the effect of EGCG on apoptosis induced by irradiation in the human keratinocytic cell line HaCaT. Irradiation by gamma-ray induced apoptosis with concomitant cleavage of caspase-3 and its in vivo substrate poly(ADP-ribose) polymerase. Treatment of cells with EGCG inhibited irradiation-induced apoptosis as detected by Hoechst staining and internucleosomal cleavage of DNA, and prevented the cleavage of these proteins by irradiation. We also found that the treatment of cells with EGCG alone suppressed cell growth and induced apoptosis in these cells. Our results suggest that EGCG inhibits irradiation-induced apoptosis by inactivating the caspase pathway in HaCaT cells. Our study also indicates that EGCG has a dual effect on the survival of these keratinocytes.

5) Study on emergency response to environmental pollution

A new system of a gamma-ray direction finder was established. The manual for detection of environmental pollution with radionuclides in radiation accidents has been completed and presented on the web site of NIRS.

Major publications:


