5. **RESEARCH CENTER FOR RADIATION EMERGENCY MEDICINE**

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**Outline of Research Career**

Dr. Akashi started his medical career at the 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 before moving to the Division of Hematology/Oncology at UCLA School of Medicine in 1987. He received a Ph.D. from Jichi Medical School in 1988. His major interests are: 1) establishment of radiation emergency medical preparedness; 2) research on radiation injuries, including molecular and cellular mechanisms; and 3) development of methods for mitigation of radiation injuries. He has treated patients of the Tokai-mura criticality accident. He took the lead and made great efforts when NIRS formed the Radiation Emergency Medical Assistance Team (REMAT) program which aims to support primary medical care when exposure to radiation or radioactive materials contamination incidents and accidents have occurred. These activities were initially focused on events overseas, but have been expanded to include Japan. He also has been providing advice and support as an expert regarding radiation emergency medicine for the TEPCO Fukushima Daiichi Nuclear Power Plant accident caused by the Great East Japan Earthquake of 2011.

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**OBJECTIVES**

This center has been assigned as the National Center for Radiation Emergency Medical Preparedness and Response by the Nuclear Disaster Prevention Plan of the Japanese government since 1980. Thus, it had the unique experience of receiving three victims heavily exposed to radiation at the JCO criticality accident of Tokai-mura in September 1999. The Center is responsible for, and has established a solid system for dealing with radiation emergencies from a medical viewpoint. Our required missions are as follows:

1. To receive victims exposed to radiation and/or contaminated with radioactive materials who require specialized diagnosis and treatment.
2. To dispatch a radiation emergency medical team to local emergency medical headquarters.
3. 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.
4. To maintain and reinforce an efficient radiation emergency medicine system under usual conditions.
5. To promote technical development and research on radiation emergency medicine.
6. To develop skilled manpower for radiation emergencies.

As an additional objective, we are carrying out fundamental research on radiation emergency medicine. Details are given elsewhere; only the subjects are presented here.

1. Research for diagnosis and treatment of exposure to high-dose radiation and/or contamination with radioactive materials.
3. Studying mechanisms of radiation injuries leading to development of new agents for treatment, with focus on the skin and gastrointestinal tract.
4. Studying indicators of radiation exposure dose from biological specimens.

**OVERVIEW**

In 1997, the Central Disaster Prevention Council (CDPC) in the Prime Minister's office added a section on emergency preparedness for dealing with nuclear power station emergencies to the Basic Plan for Disaster Prevention. This plan was reinforced in 2000 following the criticality accident at Tokai-mura in the previous year. The plan was also revised in 2008 after the Niigata-Chuetsu-Oki Earthquake of 2007 caused damage to a nuclear power plant.

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 victims heavily exposed to radiation and/or contaminated with radioactive materials due to nuclear or radiological accidents. In 2000, the NSC published the guidelines for radiation emergency medical preparedness and revised it in 2008 to clarify the role of hospitals for radiation emergencies.

From January 2004 the Research Center has served as a liaison institution of WHO/REMPAN (Radiation Emergency Medical Preparedness and Assistance Network).
Since then, the Research Center has carried out a variety of activities to maintain and enhance or strengthen the emergency preparedness system required to fulfill its role as a tertiary radiation emergency hospital.

As the latest significant activity of NIRS, we established the Radiation Emergency Medical Assistance Team (REMAT) program in January 2010. During 2010, the first activity year of the REMAT program, team members participated in not only many domestic drills but also international exercises or events such as at APEC as a comprehensive expert team dealing with radiation and nuclear accidents. Verification of the status and use of equipment and testing a communication network between the on-site team and support team at NIRS have also been performed during REMAT activities.

On 11 March 2011, a nuclear accident occurred at TEPCO Fukushima Daiichi Nuclear Power Plant of the Tokyo Electric Power Co, which was caused by a massive earthquake and accompanying tsunami. Utilizing to the fullest extent our knowledge, capabilities, experiences and REMAT’s own equipment, NIRS has been coping with the accident since the first day. The responses to the accident have become a very important mission for us and an example of the intra-organizational activities of NIRS. REMAT members have played a central role in these activities. To give prompt and accurate advice from the viewpoint of radiation emergency medicine, dose assessment or radiation protection, REMAT members and many other NIRS staff have been sent to the offsite center, J-Village which became a staging area for first responders. These are ongoing activities in the present fiscal year.

1) Network System
   The primary goal is to strengthen the institutional system to prepare for radiation emergencies by establishing three nation-wide network councils, for medicine, chromosome analysis as bio-dosimetry, and physical dosimetry.

   On 8 November, NIRS conducted a self-imposed exercise for accepting a contaminated victim. In order to enhance the cooperation among these network councils, NIRS organized a meeting to exchange opinions from the viewpoint of each specialism after the drill. After the drill, observers from the councils exchanged views at a meeting regarding how to improve performance when NIRS staff members accept contaminated patients.

1-1) Topics in the NIRS Radiation Emergency Medicine Network Council
   This is a group of experts in radiation emergency medicine or health physics for treatment of patients in cooperation with NIRS at the time of a nuclear disaster or a radiation accident. In an emergency, the cooperation involves sending an expert to NIRS, arrangement of acceptance of patients at medical facilities affiliated with the specialized organization, and providing advice. Such collaboration is expected to reinforce the functions of NIRS. This is called the Radiation Emergency Medicine Network Council to solicit cooperation when it is requested by authorities (or when NIRS considers the necessity arises) to respond to radiation emergencies. This council worked effectively at the time of the JCO criticality accident in 1999. A communication exercise was done for members of the council as a general drill for radiation emergencies on 8 November 2010 and the council annual meeting was held on 10 February 2011.

   In addition to the activities of this council, since September 2006 NIRS has had agreements on enhancement for the system of radiation emergency medical cooperation with six hospitals: The University of Tokyo Hospital; The Institute of Medical Science of The University of Tokyo; the Disaster Medical Center; the Nippon Medical School Hospital; the Nippon Medical School Chiba Hokusoh Hospital; and the Kyorin University Hospital. Some of the council’s members belong to these hospitals. The first working-level meeting with these hospitals was held on 14 February 2011.

1-2) Topics in Chromosome Network Council
   The Chromosome Network Council (CNC) forms a network among nearly ten experts on cytogenetic radiological dosimetry to strengthen its capability and establish technical standards of dose estimation methods using chromosomes. The members are chosen from six areas of Japan and they will cooperate with NIRS to carry out cytogenetic dosimetry when a severe radioactivity accident or terrorist attack involving radioactive materials occur in Japan. An inter-comparison study on the dose estimation by chromosome analysis is performed by the council members when the national drill for radiation emergencies is held every year.

   During the 5-Year Midterm Plan, a common protocol for dicentric chromosome analysis was established by the CNC. Then, in FY 2009 and FY 2010, council members tested premature chromosome condensation (PCC) analysis for high-dose exposure (10 - 30 Gy) and it was confirmed that there were still points to be improved in sample preparation for biodosimetry using the PCC method.

   In FY 2008 and FY 2010, NIRS held the “Workshop on Cytogenetic Biodosimetry” for Asian and International Science and Technology Center (ISTC) member states in cooperation with ISTC, IAEA and WHO. The CNC members presented educational lectures for participants.
from about 20 countries in both the years on biodosimetry and the past serious cases of radiation exposure in Japan. In the biennial workshops, all participants agreed to share information and to facilitate cooperation, collaborations and networking among Asian countries and member states of ISTC, especially for biodosimetry in population triage in scenarios of mass casualties. This goal will be greatly facilitated by interacting with experts who are attempting to develop the infrastructure.

1-3) Topics in Physical Dosimetry Network Council
This network council is responsible for physical dose evaluation in radiological and nuclear accidents. In FY 2010, the council participated in the exercise conducted by the Japanese government assuming a nuclear disaster at the Hamaoka Nuclear Power Plants in Shizuoka Prefecture. According to the request from the REMAT (Radiation Emergency Medical Assistant Team) sent to one of the aid stations for the public, the council members in remote places far away from the disaster site gave advice on physical dose evaluation through a real-time discussion system. In the council annual meeting, the general concept of various levels for decision making in triage and limitations in practical use were discussed.

1-4) Local organizational system for radiation emergency medicine
In Japan, the medical system for radiation emergencies is currently being constructed in accordance with disaster prevention plans of local governments where nuclear facilities have been established. Within the framework of each local nuclear disaster prevention plan, establishment of a separate collaborative system by each local government with NIRS is mandatory and the plan must specify the steps to be performed in the smooth transfer of patients from an accident site to the medical facility at NIRS, including radiation protection management.

In FY 2010, as the tertiary level hospital of radiation emergency medicine in Japan, NIRS carried out a questionnaire survey of primary and secondary level hospitals dealing with radiation emergency medicine in local governments where nuclear facilities are situated in Japan. Based on the questionnaire results, NIRS was able to summarize the current situation of their equipment and personnel necessary for treating or accepting contaminated victims.

Discussions were also held with local governments in Shizuoka, Niigata, Ibaraki, Miyagi, Hokkaido, Fukushima and Aomori Prefectures to confirm the transportation route, especially use of Japan Self Defense Force (SDF) planes or helicopters, for the victims in each prefecture. Moreover, the rapid transportation of NIRS staff members and their equipment from Chiba to each destination was newly discussed. To achieve speedy transportation of contaminated victims, information on how to cover the inside of an ambulance and a helicopter was provided to the first responders who participated in the local discussions.

NIRS organized an annual general meeting on radiation emergency medicine in Tokyo in January 2011. Medical professionals and administrative officers who are responsible for radiation and nuclear accidents from 19 local governments participated in the meeting. After the presentation from the Nuclear Safety Commission (NSC) regarding the operational new guideline of the Whole Body Counter (WBC) that will soon be made public, all the participants discussed the whole concept of the WBC and how it should be managed by each local government in line with the guideline. In addition to this discussion, NIRS shared information on the results of the hospital questionnaire survey with them and introduced its readiness for dispatching a comprehensive expert team in a radiation emergency based on the request of hospitals or local governments. Personnel from the relevant ministries and agencies such as the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour, and Welfare (MHLW), Ministry of Defense (MOD), and Fire and Disaster Management Agency (FDMA) also attended.

2) Training
The primary goal for training is the development of radiation emergency medicine skills for medical professionals and disaster response personnel; these include doctors and nurses involved in treating victims from a nuclear disaster, first responders, and nuclear establishment employees. For that purpose, NIRS holds the following courses regularly in addition to our participation in nuclear disaster prevention training, seminars on medical response, and other activities conducted by local governments to provide the relevant information and skills to deal with a radiation emergency. From FY 2010, response to malicious events and transport accidents of radioisotopes were newly added to the following course curriculums.

2-1) NIRS Course “Radiation emergency medicine (hospital course)”
In FY 2010, this 3-day course was designed for physicians, nurses, and radiological technologists who may receive victims exposed to radiation and/or contaminated with radionuclides. The course was held from 27-29 September with 26 participants. Some of them are working actively in primary or secondary levels of radiation emergency hospitals and playing an important
role in local radiation emergency systems.

In addition to this course, in response to a request from Hirosaki University School of Health Sciences, another hospital course was organized for medical professionals of this university from 8-10 March 2011. There were 19 participants in the course. Aomori Prefecture has a reprocessing factory for nuclear fuel in addition to nuclear power plants. The Hirosaki University Hospital is one of the main local hospitals and it is responsible for radiation emergency medicine in Aomori Prefecture. Upon this background, NIRS and the Hirosaki University first exchanged a memorandum of understanding (MOU) in the field of radiation emergency medicine in 2008.

2-2) NIRS Course “Radiation Emergency for first responders (pre-hospital course)”

This 3-day course was primarily designed for first responders such as fire or police department personnel, paramedics, and emergency planners at nuclear facilities. The course was held from 13-15 December 2010 with 25 participants including personnel from the Japan Coast Guard and the Japan Ground Self-Defense Force.

3) Exercises for Radiation Emergency and cooperation for the Asia-Pacific Economic Cooperation (APEC)

National and local governments annually hold nuclear energy disaster prevention drills. In FY 2010, the Japanese government conducted the drill in Shizuoka Prefecture.

NIRS dispatched REMAT members and other staff to the following domestic drills to give advice from the viewpoints of medical care and radiation protection. Communication network tests between the on-site team and support team at NIRS were performed when REMAT members were dispatched to the exercises.

a) A medical doctor and a specialist on dose assessment were sent to a nuclear energy disaster prevention drill held in Ibaraki Prefecture from 29 to 30 September 2010.

b) A medical doctor and two specialists on dose assessment of REMAT were sent to a national nuclear energy disaster prevention drill held in Shizuoka Prefecture conducted by the Ministry of Economy, Trade and Industry (METI) from 20 to 21 October 2010. In addition to the team, another medical doctor was dispatched to an offsite center in the same prefecture and a specialist on radiation emergency medicine was also sent to the Emergency Operation Center (EOC) in Tokyo.

c) REMAT members were sent to a nuclear energy disaster prevention drill in Miyagi Prefecture from 4 to 5 November 2010.

d) A specialist on dose assessment was sent to a nuclear energy disaster prevention drill held in Niigata Prefecture on 5 November 2010.

e) Two medical specialists on radiation emergency medicine were sent to a nuclear energy disaster prevention drill held in Hokkaido on 17 November 2010.

f) A medical specialist on radiation emergency medicine was sent to a nuclear energy disaster prevention drill held in Fukushima Prefecture on 26 November 2010.

g) A medical doctor and a specialist on dose assessment were sent to a nuclear energy disaster prevention drill held in Osaka Prefecture conducted by Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Under the Civil Protection Law, since FY 2005 the Cabinet Secretariat and other central government ministries such as the Ministry of Defense (MOD) have conducted joint exercises including field or map drills for civil protection with local governments. As the first field exercise due to a malicious event using a dirty bomb, a joint exercise was carried out in Mito City, Ibaraki Prefecture in January 2011. The Cabinet Secretariat and the local government asked for NIRS to cooperate in advising in various fields such as radiation emergency medicine, dose assessment, and radiation protection. Based on the request, some NIRS members worked on creating the scenario for the exercise from an early stage. In order to support local medical staff, two REMATs were dispatched to the Mito-Saiseikai Hospital, which normally has not been nominated as a primary or secondary hospital in this area but was newly designated to accept many contaminated victims for this exercise. One team from REMAT was transported by a Self-Defense Force’s helicopter and another moved by a monitoring car. Besides these field players, a REMAT medical doctor observed the exercise and evaluated the activities conducted by both national and prefectural governments as an evaluating committee member.

From 7 to 8 February 2011, in addition to the above exercises, NIRS conducted an exercise with Hirosaki University and the Japan Nuclear Fuel Ltd. (JNFL) which has a reprocessing factory for nuclear fuel in Aomori Prefecture. In this drill, we developed the scenario and held the drill which contained some blind elements. This scenario included transportation from JNFL to Hirosaki University of a patient who had possible internal exposure. A medical doctor and two specialists on dose assessment and radiation protection were dispatched from NIRS to Hirosaki by train and a monitoring car. A TV conference between NIRS headquarters and university staff was also held as part of the exercise.
To improve our own skills, NIRS also held three self-imposed exercises for the treatment of contaminated victims in July and November 2010. Two of the exercises were focused on the treatment of internal contamination by alpha emitters.

From 12 to 15 November 2010, the Asia-Pacific Economic Cooperation Conference (APEC) summit meeting and ministerial-level meeting were held in Yokohama. The Japanese government established a local headquarters near the venue to safeguard foreign dignitaries in the case of various emergencies. On the basis of requests from the Ministry of Health, Labour and Welfare (MHLW), NIRS assembled response teams to prepare for radiation emergency medicine and created a REMAT program task force at NIRS. One team from the REMAT program that consisted of a medical doctor, two health physicists and a specialist on radiation protection were dispatched to the local headquarters. Two others were also ready to respond for the general public if a malicious event with radioactive materials release occurred at Haneda or Narita Airports.

4) Follow-up Studies

The center continues to carry out medical follow-up for victims who were exposed to radiation in the thermo-nuclear weapon tests on Bikini Atoll, and the surviving JCO accident victim.

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

On 1 March 1954, the 23 crew members (18 to 39 years old at the time) of the Japanese fishing vessel Daigo Fukuryu Maru (which means "Lucky Dragon") from Yaizu City, Shizuoka Prefecture saw a bright light in the South Pacific resembling a sunrise. Seven or eight minutes later there was a terrific sound. They did not know what it was at the time. The blast, equivalent to about 12 million tons of TNT, was 750 to 1,000 times more powerful than the atomic bomb released over Hiroshima. All 23 people were hospitalized after returning to Japan. One of them died of liver failure seven months later. Several hundred inhabitants of the Marshall Islands in the Pacific, as well as nearly 30 U.S. army personnel involved in the tests, were also injured from the nuclear fallout. Their medical follow-up aims at studying late radiation effects by examining the health states of these victims over a long period of time. The follow-up examinations that have been conducted for 50 years provide important information. The type of exposure was external and also internal, although internal doses were thought to be relatively small. The estimated whole body doses were 1.7 to 6.9 Gy. Among 23 victims, 14 have already died. In FY 2010, a medical check-up of survivors was conducted for 6 victims at Yaizu City Hospital. Details on the cause of death are as follows: 6 died of liver cancer, 2 of liver cirrhosis, 1 of liver fibrosis, 2 of colon cancer, 1 of heart failure, 1 in a traffic accident, and 1 of an aortic aneurysm rupture. Malignancies were suspected in two of these people. Many of them have evidence of infection with hepatitis viruses. Since all 23 victims received transfusions in 1954, transfusion might be the most important factor for infection by hepatitis viruses, although transfusion was one of the best treatments for bone marrow suppression at that time.

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

Thorotrast is an alpha emitting thorium dioxide colloid, which was used clinically in the 1930s and 1940s as a radiographic contrast medium. It was injected intravascularly for visualization of vascular structures. Long-term retention of thorotrast in the reticulo-endothelial system, in the liver, spleen and bone marrow produces lifetime alpha particle irradiation of these organs and considerable epidemiological follow-up work has been performed. The major cohorts that can be used for risk evaluation are German, Danish and Japanese patients subjected to thorotrast. The incidence of leukemia has increased among these persons. 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. 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 carcinogenesis, and elucidates the effects of long-term internal radiation exposure on human bodies. There were no patients who had a medical check-up this year.

5) Database

Since radiation accidents requiring medical care are extremely rare, the medical information must be collected from each accident and accumulated to help medical professionals to make decisions for strategies to treat victims, and establish and improve therapeutic methods. A medical database including the cases of radiation exposure at Bikini Atoll in the South Pacific and cases of thorotrastosis is being constructed. Today, there are many database systems on radiation accidents and their victims, but most are only accessible from the related countries. Under the supervision of the WHO, an international program called REMPAN 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 Daigo Fukuryu Maru accident in the SEARCH database. In addition, the center is constructing a database by collecting medical data of the victims of radiation accidents and exchanging information with countries that have developed radiation accident medicine.

6) Operation of 24/7 Radiation Emergency Call System

Since FY 2008, the NIRS has been operating the 24/7 on call radiation emergency system for hospitals and first responders, including fire department personnel. This system is for direct or consultative assistance regarding medical and health physics problems associated with radiation or nuclear accidents. This consultation on a 24-hour basis can be reached by phone. After usual business hours, the phone call is automatically transferred to 3 or 4 staff members (which include a medical doctor and a health physicist) of the Research Center for Radiation Emergency Medicine.

7) Other consultation for health effects of radiation

The NIRS receives consultations on health effect of radiation. From 1 April 2010 to 10 March 2011, we received consultations on 24 cases. Of those, 3 cases were consultations on radiation exposure; 18 were consultations on doubtful radiation exposure; and 3, miscellaneous.

On 11 March 2011, Northeastern Japan was struck by an incredibly strong earthquake, which was followed by the nuclear accident at the TEPCO Fukushima Daiichi Nuclear Power Plant. The NIRS has received many inquiries on radiation and radioactive materials by first responders, medical experts, and government officials since 11 March 2011. We were consulted 421 times on the 24/7 radiation emergency call system from 11 to 31 March 2011. But in addition to the calls from experts, the number of callers from the general public increased sharply, so the NIRS set up another phone service for the public to answer questions and reduce anxiety.

The NIRS disseminated information through its homepage; for example, simple methods of decontamination for radioactive materials and correction of misinformation on the internet regarding commercially available products containing iodine, that were purported to provide radiation protection. Government ministries, particularly the Ministry of Foreign Affairs of Japan (MOFA) and other public administrations introduced NIRS’s website as a useful source of accurate information. Foreign embassies in Japan also introduced NIRS’s website as a reliable information source to their citizens residing in Japan.

8) International Cooperation

8-1) Training courses for foreign medical professionals organized by NIRS

Upon a request from the Korea Institute of Radiological & Medical Sciences (KIRAMS), the NIRS Training Course for Korean Medical Professionals on Radiation Emergency Medical Preparedness was held from 7-10 September and from 16-18 November 2010.

8-2) International seminars/workshops

a) The NIRS-KIRAMS Joint Seminar on Radiation Emergency Medicine 2010 was held from 6-8 October 2010 by KIRAMS and NIRS.

b) NIRS-IAEA Workshop on Cytogenetic Biodosimetry for Asia 2011 & NIRS-ISTC Workshop on Cytogenetic Biodosimetry in cooperation with WHO was held from 26-27 January 2011.

c) The NSC/NIRS workshop on medical response to nuclear accidents in Asia was held from 28 February to 2 March 2011 by the Nuclear Safety Commission (NSC) and NIRS. As part of this workshop, information on internal contamination and other topics was exchanged among all 14 people (10 from 10 Asian countries, 3 from other area countries, and 1 from IAEA) attended.

8-3) Invited lectures

NIRS staff members were invited to give lectures in the following meetings and training courses.

a) IAEA Training Course on Medical Response to Radiation Emergencies held in Teheran, Iran, 20-28 May 2010.

b) IAEA National Training Workshops on Medical Response to Radiological Emergencies held in Bucharest, Romania, 22-27 June 2010.


d) Invited lecture for Korean medical experts from KIRAMS held in Seoul, Korea, 7-10 September and 16-18 November 2010.

e) VAEI/IAEA Follow-up Training Course on “Nuclear and Radiological Emergency Preparedness” held in Hanoi, Viet Nam from 27 October to 2 November 2010.

f) Technical Support Working Group(TSWG) held in Florida, USA from 28 November to 3 December 2010.

g) The 13th Coordination and Planning Meeting of the WHO REMPAN Collaborating Centers and Liaison
Institutions held in Nagasaki City, Japan, 15-18 February 2011.

8-4) International meetings / conferences
NIRS staff member attended the following meeting.

a) 2nd International MELODI Workshop, Cite Internationall Universitaire de Paris, France, 18-20 October 2010.

8-5) Members of international committees
NIRS staff members participated in the following committees.

a) Planning meeting for GHSAG TABLE TOP EXERCISE held in Luxembourg, Grand Duchy of Luxembourg, 10 June 2010.


c) The 2nd Planning Meeting for EXERCISE ECLIPSE held in Luxembourg, Grand Duchy of Luxembourg, 2 September 2010 (Video attendant).

d) The 2nd meeting of WHO BioDoseNet held in Mandelieu-La Napoule, France, 10 October 2010.

e) IABERD meeting held in Mandelieu-La-Napoule, France, 12 October 2010.

f) Meeting on International Organization for Standardization held in Mandelieu-La-Napoule, France, 14-15 October 2010.

g) Consultants’ Meeting on Strengthening Biological Dosimetry in IAEA Member States held in Vienna, Austria, 10-12 November 2010.

h) ICRU Annual Meeting held in Essen, Germany, 14-20 November 2010.

8-6) Other overseas visitors

a) A researcher from Washington State University was invited to NIRS to give a lecture and to exchange information about the recent status of radiation emergency medicine on 27 May 2010.

b) Two researchers and an administrator from KIRAMS were visited to NIRS on 17 July 2010 to exchange information and see our facilities.

c) A medical doctor from Sri Lanka stayed to work in improving the network of radiation emergency medicine in Asia from September to December 2010.

d) A medical doctor from Germany visited NIRS on 15 February 2011 to give two lectures on radiation protection for accepting patients with internal contamination and on information regarding public response in case of radiological accidents in Germany.

e) Two cadets from a school of medicine in Germany visited and we gave guidance about radiation emergency medicine from 22-23 February 2011.

8-7) Exchange of human resources and information

a) An NIRS medical doctor worked at the IAEA Incident and Emergency Centre (IEC) to collect information from February 2010 to March 2011.

b) An NIRS member worked at the IAEA to collect information from February 2010 to March 2011.

c) An NIRS member went to the Institute de Radioprotection et de Sûreté Nucléaire (IRSN) to learn about bioassay techniques from April 2010 to March 2011.

d) Some NIRS staff and REMAT members attended an international antiterrorism tabletop exercise hosted by the Global Health Security Action Group (GHSAG) from 26-27 October 2010.

e) A medical doctor and a clerk from KIRAMS observed Ibaraki Prefecture’s drill, in which NIRS participated, to protect civilians hosted by the Cabinet Secretary on 30 January 2011.

8-8) Memorandum of Understanding

As of March 2011, NIRS has signed MOUs on radiation emergency medicine with the following overseas organizations.

a) Korea Institute of Radiological & Medical Sciences (KIRAMS), Seoul, Korea, in effect since 16 November 2004.

b) National Institute for Radiological Protection (NIRP), Beijing, China, in effect since 27 November 2007.

c) Institute de Radioprotection et de Surete Nucléaire (IRSN), Fontenay-aux-Roses, France, in effect since 28 October 2008.

d) King Abdulaziz City for Science and Technology (KACST), Riyadh, Saudi Arabia, in effect since March 2010.

8-9) Activities in the REMAT (Radiation Emergency Medical Assistance Team) program

Today, radiation is widely used in our lives. Potential sources of radiation accidents include industrial radiography, therapeutic devices, sterilizers, transportation accidents, and nuclear power plants; devices used for industrial radiography and accelerators are frequent sources of external exposure accidents. However, once an accident involving radiation occurs, much anxiety and fear arise in society, based on the fact that such accidents, fortunately, are not common; but then, paradoxically, there are few chances to become knowledgeable about radiological accidents. Radiation cannot be seen by the human eye, smelled, heard, or otherwise detected by our normal senses, nor do symptoms or signs appear soon after exposure. Therefore, dose assessment is essential for taking care of patients involved in radiation accidents, providing appropriate treatment including administra-
tion of decontamination agents. Since the practice of medicine is based on science as well as past experience, the knowledge of triage, assessment, initial diagnostic methods, and general treatment protocols has to be shared among medical professionals throughout the world.

In FY 2010, the Radiation Emergency Medical Assistant Team (REMAT) program was established at the NIRS. As of March 2011, there are 42 members, including physicians, nurses, radiation protection experts, and health physicists ready to respond to radiation emergencies. As the first overseas activity, REMAT participated in an exercise program on radiation monitoring near the Chernobyl disaster area in June 2010. The program was organized by the European Centre of Technological Safety, Ukraine. And also the REMAT program dispatched the appropriate staff members to various exercises conducted against a severe accident of a nuclear power plant or terrorist attack using radiological substances. In those exercises, we reconfirmed the great importance of communication between on site staff and staff at NIRS. On 11 March 2011, the Great Northeast Japan earthquake occurred, followed by the Fukushima nuclear disaster. REMAT promptly dispatched three staff members—a physician, a health physicist and a nurse—to the off-site center established in Fukushima, and emergency action was quickly activated.

8-10) Other topics

Staff members attended the IAEA general conference and introduced the activities of the Radiation Emergency Medical Assistance Team (REMAT) program which was established in January 2010.

9) Radiation Emergency Medicine Cooperative Research Facility

The Radiation Toxicology Building was constructed in 1985 and research using animals for internal contamination with Pu or other radioactive materials was conducted there. After completion of inhalation experiments, a future plan for the building was discussed within NIRS.

Considering the situation in Japan including the expectations of the Nuclear Safety Commission regarding research on radiation exposure to Pu and operation starting at the Rokkasho Reprocessing Plant, NIRS decided to reactivate the facility for a new research direction in 2009. The building was renamed the Radiation Emergency Medicine Cooperative Research Facility. To facilitate the project, the Promotion Section for Radiation Emergency Medicine Cooperative Research Facility was created in April 2010. The research plans include studies on kinetics of aerosol and dose assessment, dose assessment by measurements such as chemical analysis and bioassay, and acute-sub acute toxicity assessments of actinides and de-cooperation drugs. Replacement and repair of deteriorated facilities and equipment were started, including renewal of a scrubber for an incinerator. An animal raising hood with glove-box type air sealing was also replaced in 2011.

Meanwhile some researchers conducted other work during this time. Actinide safety research (mainly, U and Pu) including experimental toxicology, decontamination research, dosimetry research, and environmental dynamics and molecular carcinogenesis, have been conducted at the facility.

For internal decontamination research in radiation emergency medicine, acute toxicity of actinides, and effect of agents on removal of actinides contamination were studied. This study focused on (1) the examination of the acute toxicity of uranium in simulated wounds using rat model and (2) the decontamination effects of various agents including chelating substances in this model.
**5.1 The Study of Medical Treatment for High Dose Exposure**

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**Outline of Research Career**

Dr. Akashi started his medical career at the 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 before moving to the Division of Hematology/Oncology at UCLA School of Medicine in 1987. He received a Ph.D. from Jichi Medical School in 1988. His major interests are: 1) establishment of radiation emergency medical preparedness; 2) research on radiation injuries, including molecular and cellular mechanisms; and 3) development of methods for mitigation of radiation injuries.

When the Tokai-mura criticality accident occurred in 1999, he treated the patients who were taken to NIRS. He also has been providing advice and support as an expert regarding radiation emergency medicine for the Fukushima Daiichi Nuclear Power Plant accident caused by the Great East Japan Earthquake of 2011.

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**Objectives**

This department conducts studies that are usually not performed by other research institutions, emphasizing the diagnosis and treatment of radiation injuries due to high dose exposure. The members try to clarify the mechanism of injuries in cells and tissues exposed to high doses of radiation and its effects on survival, repair, and maintenance of function. In these studies, we are evaluating candidate substances for therapeutic drugs particularly for gastrointestinal and skin injuries. For gastrointestinal injuries due to radiation, we use experimental animals, primary cultured cells, and tissues to develop quantitative evaluation systems. In addition, we study medical treatments with cytokines, natural products, and synthetic compounds that decrease the severity of injury.

To develop accurate diagnostic dose assessments for high-dose exposure to radiation, we also try to find markers for radiation exposure from bio-molecules contained in samples which can be collected less invasively, such as blood. We are attempting to determine genes, proteins, and other constituents in a living body that can provide a guide for treatment to radiation exposure.

**Progress of Research in the 2nd Mid-term Plan**

1) Study on treatment for intestinal injuries due to high doses of radiation

Several members of the fibroblast growth factor (FGF) family have potential to protect the intestine against the side-effects of radiation therapy. FGF1 is capable of signaling through all subtypes of FGF receptors (FGFRs). Therefore, we compared the protective activity of FGF1 and other FGFs, and examined the profiles of FGFR expression in the jejunum of BALB/c mice given total body irradiation (TBI) with γ-rays. The results revealed that FGF1 was more potent than FGF7 or FGF10 for protection of the intestine against radiation exposure, and suggested that the profiles of FGFR expression in the intestine favored the FGF1 signaling pathway before and during the initial period after irradiation. In contrast, an FGF1:FGF2 chimera (FGFC) was created and it showed greater structural stability than FGF1. Therefore, FGFC was expected to have greater biological activity in vivo. We evaluated and compared the protective activity of FGFC and FGF1 against radiation-induced intestinal injuries. Consequently, we found that FGFC strongly enhanced radioprotection with the induction of epithelial proliferation without exogenous heparin after irradiation and FGFC was useful in clinical applications for both the prevention and post-treatment of radiation injuries.

2) Effect of FGFC chimeric protein in mouse survival after high-dose irradiation

FGFC shows a higher radioprotection effect on mice intestine as compared to FGF1. However, the effect of FGFC on the survival of irradiated mice is unknown. In this study, we compared the effects of FGF1 and FGFC on their survivals after irradiation using BALB/c mice. FGF or saline was administrated intraperitoneally to mice before or after whole body γ-irradiation. Administration of each FGF to mice before irradiation with 7 Gy (LD100/30) increased the survival rates significantly as compared to those of control mice. However, there was no difference between mice with FGFC and FGF1. When mice were exposed to irradiation with a higher dose, 11 Gy (LD100/10), neither bone marrow transplantation (BMT) after irradiation or administration before irradiation improved the survival rates. In contrast, combination of pre-treatment with FGFC and BMT after irradiation
significantly improved the survival rates, whereas the combination of FGF1 and BMT did not affect the rates in these mice. These results suggest that FGFC has a synergistic effect with BMT on the survivals in heavily irradiated mice.

3) A cell-permeable C-terminal PIDD fragment inhibits ionizing radiation-induced activation of pro-death caspase-2

PIDD (p53-induced protein with a death domain) plays a critical role in the activation of caspase-2 to trigger apoptosis induced by DNA damage through the formation of a so-called PIDDosome, which contains the adaptor protein RAIDD and caspase-2. We found that transcription of PIDD was induced after exposure to ionizing radiation in rat small intestinal epithelial cell line (IEC6) cells. Yeast two-hybrid analysis indicated that the death domain of rat PIDD interacts with RAIDD. Interestingly, a rat C-terminal PIDD fragment (residues 773-917) containing the death domain interacts with RAIDD much more tightly than the longer PIDD fragment (residues 610-917). We purified a recombinant PIDD (773-917) fragment fused with a basic 11-amino acid peptide (TAT) derived from the HIV-Tat protein which facilitates uptake of the protein into mammalian cells with high efficiency. When PIDD (773-917)-TAT was added to the IEC6 cells, the protein was efficiently delivered into the cells within an hour. Furthermore, we observed that ionizing radiation-induced activation of caspase-2 and caspase-9 was inhibited when PIDD (773-917)-TAT was added to the IEC6 cells. These results suggest that PIDD (773-917)-TAT can protect gastrointestinal cells from ionizing radiation-induced cell death.

4) Cell-permeable inhibitor of apoptosis (IAP) proteins inhibits radiation-induced cell death

Gastrointestinal syndrome after high-dose radiation exposure is caused by gastrointestinal apoptosis. Inhibitor of apoptosis (IAP) proteins, such as X-linked inhibitor of apoptosis (XIAP) and cellular inhibitor of apoptosis protein 1 and 2 (cIAP1 and 2), are intrinsic cellular inhibitors of apoptosis. In order to prevent gastrointestinal syndrome, we purified cell-permeable recombinant XIAP (full-length, BIR2 domain, and BIR3-RING domain with or without mutations of autoubiquitilation sites) and cIAP2 proteins fused with a protein transduction sequence (TAT) derived from the HIV-Tat protein and examined the effects of these proteins on radiation-induced cell death in rat small intestinal epithelial cell line (IEC6) cells. When the TAT-conjugated IAP proteins were added to IEC6 cells, these proteins were delivered into the cells and inhibited apoptosis after irradiation. Furthermore, we found new protein modifications of IAP proteins. Our results suggest that the cell-permeable IAP proteins may be useful for protection of gastrointestinal cells from radiation-induced cell death. Future analysis of the protein modifications may facilitate improvement of the inhibitory efficacy of the TAT-conjugated IAP proteins.

5) Modification of radioprotective effects of heat-killed Lactobacillus casei by glucocorticoids mediated by proinflammatory cytokines in mouse

Administration of proinflammatory cytokines in experimental animals 1 day before lethal dose of irradiation leads to increased survival rate via alteration of hematopoietic progenitor cells to increase resistance against radiation, and they are recognized as radioprotectors. A single injection of bacterial constituents such as heat-killed Lactobacillus casei (HLC) to C3H/He mouse 24 hours before x-irradiation of the LD50 dose of 8.0Gy also show similar radioprotective action. We found that administration of HLC effectively increases the level of interleukin (IL)-1 beta as compared to Bacillus subtilis and Escherichia coli in the mouse species. Since HLC stimulates inflammation in early immune responses, effects of pharmaceutical drugs modifying the early process were compared. The increase in both blood IL-1 beta levels and survival rates by HLC were simultaneously accelerated by coadministration of mineralocorticoid and inhibited by glucocorticoids, known as anti-inflammatory drugs. In contrast, no similar modification in the IL-1 beta levels and survival rates by HLC were found by coinjection of non-steroidal anti-inflammatory or anti-rheumatoid drugs. This suggests that expected action of inflammation-related radioprotectors can be controlled by the coadministration of drugs at least in C3H/He mice, based on consideration of their pharmacological properties.

6) Radiation dose-dependent augmentation of mRNA levels for DNA damage-induced genes elicited by accurate real-time RT-PCR quantification and the evidence of the effects of circadian rhythm in mouse

We established a method to quantify mRNA levels of DNA damage-induced genes as indicators of growth-arrest (p21 and mdm2) and of apoptosis (bax and puma) with high reproducibility and accuracy based on real-time RT-PCR. Messages for p21 and mdm2 were augmented before growth-arrest and a puma mRNA was increased before apoptosis in RAW264.7. Their peak levels were dependent upon x-ray irradiation doses between 0.1 to 3.0Gy. Similarly, the relative RNA levels of p21, mdm2, bax, and puma per GAPDH also increased dose-dependently in peripheral blood and bone marrow cells isolated from whole-body-irradiated mice in the ranges from 0.1 to
1.0 Gy of x-ray.

Generally, quantitative study using cells isolated from the living body of humans and experimental animals is difficult, because they are altered by a physiological oscillation such as circadian rhythm. The induction levels in peripheral blood of all the above-mentioned messages were reduced by half after nighttime irradiation as compared with daytime irradiation of mouse. In marrow cells, nighttime irradiation enhanced the p21 and mdm2 mRNA levels more than daytime irradiation. No significant difference in bax or puma mRNA levels was observed between nighttime and daytime irradiation in marrow cells. This suggests that the damage in hematopoietic cells can be quantitatively analyzed using apoptosis-related genes in marrow and that modulation between diurnal and nocturnal irradiation is remarkable in peripheral blood.

7) Regeneration of mucosa in small intestine damaged by high-dose radiation is accelerated by anabolic steroids and inhibited by follicle hormone.

Mucosal damage in the small intestine is a serious problem after accidental or clinical high-dose radiation exposure. To examine substances to ameliorate the damage by post-irradiation administration, we focused on the regeneration process after irradiation of the intestine. Using an in vitro experiment in IEC-6 epithelial cells of rat intestinal mucosa, the effects of various sex hormones on the growth were compared. The proliferation was stimulated by steroids with anabolic action including 19-nortestosterone (nandrolone) and androgens, and was inhibited by high concentrations of follicle hormone, such as estradiol. The significant life-saving effects of nandrolone ester by a single injection 24h after exposure was confirmed by in vivo experiments using abdominally irradiated mice at the LD50 dose of 15.7 Gy of x-ray. Regeneration indicators such as microcolonies of proliferating cells visualized by bromodeoxy uridine staining at day 5 and c-myb mRNA expression levels at day 4 in the small intestinal mucosa were enhanced by nandrolone administration, suggesting that the drug contributes to repair of mucosa after irradiation. A similar life-saving effect was not found in native androgens in vivo. As in the in vitro experiment, treatment of abdominally irradiated mice with estradiol ester decreased these regeneration indicators and the survival rate. These results suggest the effectiveness of anabolic steroid as well as the importance of manipulation of steroid receptors in the recovery of mucosa in small intestine damaged by high-dose radiation.

**Major Publications**


5.2. RESEARCH ON RADIATION DOSE ASSESSMENT

Yuji Yamada, Ph.D.
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Outline of Research Career
Dr. Yamada received a Ph.D. from Nagoya University in 1989 for his study on collection performance of high efficiency particulate air filters. At NIRS, he has accumulated over 30 years of experience in research on radioactive aerosols and their internal exposure. Between 1986 and 1987 he was at the Inhalation Toxicology Research Institute (ITRI) of the Lovelace Foundation, USA as a visiting scientist where he studied aerosol deposition within the respiratory tract.

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OBJECTIVES

Radiation accidents can be divided into those that result in external exposure and those that result in internal exposure. For severe accidents, bone marrow transplantation may be considered depending on the external exposure dose received, or drug administration may also be considered to inhibit deposition and promote excretion of radioactive substances incorporated into the body. Dose assessment of victims in radiation accidents must be made within a short time, taking into account the details of the accident, to estimate the radiation effects and to initiate appropriate medical treatment.

Major subjects in radiation dose assessment research are: 1) collection and analysis of information on the occurrence of radiation accidents, radiation type, and radioactivity; 2) determination and evaluation of the amount of radioactivity in the body and excreta; and 3) biological evaluation of the effects resulting from exposure on the body. Our aims are to shorten the time needed for analysis and dose determination, and to improve the accuracy of comprehensive assessment, which combines physical and biological dose assessments.

In the area of radiation emergency medicine, we have made basic and application studies for clinical use of agents in removing radionuclides, especially alpha emitters like plutonium or uranium that are incorporated into the body.

PROGRESS OF RESEARCH

1) Chromosome aberration analysis for dose assessment

The National Institute of Radiological Sciences (NIRS) is the national center for radiation emergency medical preparedness in the nuclear disaster prevention system of Japan. Biodosimetry is a method for accurately estimating unknown radiological doses to individuals following radiological or nuclear accidents.

Among several methods for biodosimetry, dicentric chromosome analysis (DCA) based on chromosome morphology has been used since the mid 1960s and is called the gold standard. By the end of FY 2010, we had established a practical and more rapid system based on DCA using a microscopic image analysis instrument equipped with automatic cell-finding and cell-capturing functions. We have confirmed the system accuracy, its limitations, and the time required for dose estimation.

For analyzing radiation-induced chromosome aberrations based on DNA sequences, we have introduced and developed a fluorescence in situ hybridization (FISH) technique. By using centromere- and telomere-specific peptide nucleic acid (PNA) probes, more accurate detection of multi-centric chromosomes as presented by dicentrics has been made possible (Fig. 5.1). By Multiplex FISH (M-FISH) using chromosome paints which identify 22 autosomes and the sex chromosomes X and Y, we detected more complex aberrations in irradiated cells and found that the actual frequency of chromosome aberration caused by radiation exposure was much higher. Since M-FISH is useful for detecting stable aberrations such as translocation, we will apply it to long-term follow-up studies and retrospective studies for past radiological accidents in Japan in the next stage.
2) Development of rapid biological dose estimation method for partial body exposure

Chromosomal aberrations in the peripheral lymphocytes are the most reliable indicators for biological dose estimation of radiation exposure. The conventional method for estimating this dose uses score marker aberrations, such as dicentric and ring chromosomes in lymphocytes. However, because lymphocytes circulate in the peripheral blood, the dose estimated from these dicentric or ring values is the mean dose of whole-body cumulative radiation exposure. Therefore, in the case of partial body exposure, it is difficult to estimate the partial dose of radiation by this method. In order to establish an assay system to estimate the radiation dose in the case of partial body exposure, we used the human hair root as the target organ for dose estimation. The comet assay was applied for the detection of DNA damage in the hair root cells after irradiation and we detected a slight relationship between tail length indicating DNA damage and irradiated dose. This suggests the possibility that the comet assay in hair root cells will be useful for positional identification in partial body exposure.

3) Development of an early detection system for unknown radiation in a radiological emergency

Two types of early detection systems concerning unknown radionuclides and unknown energies were developed aiming at prompt personal dose evaluation in a radiation emergency. One is an alpha, beta and gamma surface contamination measuring system corresponding to contamination such as due to fission products. This system consists of three detectors, i.e. the EJ-204 type plastic scintillator is inserted as a beta radiation detector through an electron shield into the CsI(Tl) scintillator used as a gamma radiation detector and ZnS(Ag) scintillator is painted on the surface of the plastic scintillator as an alpha radiation detector. All their luminescences are measured with one photomultiplier tube set on the same axis. The separate measurement of each radiation type from mixed contamination becomes possible in real time by synchronization of the time spectrum and the energy spectrum from each scintillator.

The second detection system is an external dose evaluation system for use in a mixed gamma radiation field. It is composed of a physical phantom, a phantom insertion type semi-conductor detector (Fig. 5.2), and the GUI type Monte Carlo calculation code. The Si detector (1 cm in diameter) on the following amplifier substrate designed for the Compton spectrum measurement is inserted into the tissue-equivalent medium. The detector which can identify radiation up to the $^{60}$Co energy region is inserted into the main internal organs position in a physical phantom. It can measure the equivalent dose based on the response function in a gamma radiation field. This detector is used to get bench mark values in the Monte Carlo calculation under various conditions. The effective dose evaluation by this Monte Carlo calculation code is carried out based on the initial information about the exposure geometry in an unequal external exposure accident.

4) Nasal swab for alpha emitters

Nasal swabs are useful to confirm the possibility of internal intake just after accidental inhalation of alpha emitters. The swabs are also expected to be a useful method for rapid dose assessment. To improve the first estimation of intake activity, the quality of a nasal swab measurement was experimentally investigated. Particle diameter is important information for dose assessment. The dose conversion factor for the $^{239}$PuO$_2$ particle sampling filter was used as a beta radiation detector and $\text{ZnS(Ag)}$ scintillator is painted on the surface of the plastic scintillator as an alpha radiation detector. All their luminescences are measured with one photomultiplier tube set on the same axis. The separate measurement of each radiation type from mixed contamination becomes possible in real time by synchronization of the time spectrum and the energy spectrum from each scintillator.

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examined. An especially thick film was coated onto a filter which was exposed for 60 days. Alpha tracks were counted for each particle. Particle diameter was calculated based on the number of tracks. The calculated particle diameter was equivalent to the measured particle diameter obtained by an aerosol measuring instrument. When a simulation was done based on the result, the dose assessment for a particle diameter of 5 µm could be estimated in a 10 minute film exposure when the assumed particles were $^{239}$PuO$_2$. These results indicated that rapid dose estimation would be expected using the combination of the DCFnasal and track measurements.

5) Development of in vivo measurements

It is important to estimate the amounts and decide the types of radionuclides from outside the body at the time of accidental intake of radionuclide. Especially, when transuranic elements are inhaled, the low energy LX-rays must be measured; these are difficult to measure accurately with a lung monitor. The Lawrence Livermore National Laboratory phantom (LLNL phantom) is used to calibrate the lung monitor. But its size is very different from the physical size of a Japanese adult. So, we developed the phantom that fits the Japanese physical size. The formation of the lung models in the phantom agreed with MRI data for the lung of Japanese individuals as well, and the characteristics for radiation penetration also had good agreement. The distribution of the material was confirmed by X-ray tomography and cutting of the lung model. As a result, the composition was seen to be almost the same independent of the position. The radioactive lung models were made by uniformly diffusing a radio-source in the polyurethane phantom by foamed. One of them was also cut. Because the radioactivity was about 3 kBq for the whole lung model, it sections were positioned closely together on an imaging plate surrounded by a blackout curtain inside a low background room and the 59.5keV gamma rays from Am-241 were observed. Moreover, we made the mapping measurement that rolled a 1mm lead collimator in a one-inch NaI detector, too. From the results, the uniformity and the physical structure of the radiation source were proven. Finally, we compared the model with the LLNL phantom. But no big difference was observed in counting efficiency.

6) Effects of chelation therapy and new chelating agents on removal of uranium in a simulated wounds model of rats

A study on acute uranium toxicity clarified that the biochemical markers of renal function, such as N acetyl-beta-D-glucosaminidase, blood urea nitrogen and creatinine, are useful clinical indicators for renal damage, and osteocalcin is a useful indicator for bone damages in rats. A study on the removal of uranium contamination clarified that catechol-3,6-bis (methyleneimodiacetic acid) (CBMDIA), ethydonate disodium (EHBP), and lactoferrin were effective, however 1,2 dimethyl-3-hidroxypyrid-4-one (deferipron), sodium bicarbonate, diuretic agents, transfusion showed no effects. In addition, no promising compounds have been found yet among newly synthesized chelating agents.

**MAJOR PUBLICATIONS**
