2. Marrow Donor Programme in Japan

Shigetaka Asano, M.D., D.M.Sci.
Institute of Medical Science, University of Tokyo
Tokyo, Japan

SUMMARY

The Japan marrow donor programme has been working well as the largest one in the Asian-Pacific area. However there remain many problems to be solved concerning unrelated bone marrow transplantation (UBMT) carried out through the programme. We should remind that UBMT is still at the investigational stage.

Organizations for Marrow Donor Programme

Almost 3 years have passed since the public bone marrow donor programme for the purpose to fairly provide a chance to patients who want to receive unrelated bone marrow transplantation (UBMT) was founded in Japan (1). The programme has been conducted by cooperation of two organizations both of which were established on the initiative of the Japanese Ministry of Health and Welfare (MHW): the Japan Marrow Donor Foundation (JMDF) having the responsibility both for the donor and recipient registration and the donor recruitment, and the Japanese Red Cross (JRC) having the responsibility for the human leukocyte antigen (HLA) typing of registered volunteer potential donors and functioning as a central donors' HLA data bank

Process of Donor Recruitment

The donor recruitment process is to be initiated by being submitted the donor search request form to JMDF by any physician in accredited marrow transplantation centers worldwide. On receiving the request, the JMDF secretariat investigates the patient eligibility in a businesslike manner, according to the Guideline agreed in the Central Coordination Committee of JMDF. If the request is judged as acceptable, the secretariat asks JRC to search for the potential donors whose HLA-A, -B and -DR loci are matching with the patient's ones in the computerized secret files and to send a list of several compatible donors to the secretariat. On receiving it, the secretariat asks some of the qualified JMDF coordinators who are working in the same area as the potential donors' places to contact with the donor candidates for confirming the medical eligibilities In this contact, various examinations are scheduled at the donors' place. At this time, the HLA class II molecular oligonucleotide typing, if necessary, can be now asked to JRC Based on the information of each donor candidate obtained by the coordinators, the JMDF secretariat ultimately selects one most suitable potential donor among them together with a desirable marrow harvesting center, and informs it to the selected donor. The marrow harvesting center then starts to communicate the donor in collaboration with the coordinator and the patient physician for making a UBMT schedule for the patient. At all the above steps, the rights of both donor and recipient to privacy and confidentiality are respected at all times. In addition, the identity of the donor and recipient shall not be disclosed even after finishing the transplantation.

Status of Donor Registration

The above programme has been so far going well as expected, by receiving the financial support from many voluntary individuals and groups. Figure 1 shows the monthly change in the number of registered donor candidates. The accumulated number has reached approximately 70,000 as of August 1995 (shown as a dotted line), most of whom have been already typed for HLA-A, -B and -DR. Characteristically, the donor pool consists exclusively of Japanese (more than 99.9%). The donor pool in Japan is the largest in the Asia-Pacific area and will be able to be used for recipients of oriental origin worldwide.

Status of Recipient Registration

As shown in Figure 2, the accumulated number of patients who received UBMT through the programme has been gradually increasing in parallel with the potential donor size. At present (as of February 1996) the number has already exceeded 700. It means that one patient is now receiving UBMT everyday The data as of August 1995

show that the disease distributions of the recipients are 43% with acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML), 35% with chronic myeloid leukemia (CML), 11% with severe aplastic anemia (SAA); 6% with myelodysplastic syndromes (MDS) and 5% with the other diseases (Figure 3) The younger patients tend to receive more GVHD (Figure 4) and the regional difference is clear (Figure 5).

Results of UBMT

The transplantation results through the programme in Japan have been recently analyzed by the JMDF secretariat (Figure 6-8). The actuarial probabilities of survival at 2 years are 43% with ALL (n=84) and AML (n=106), 40% with CML (n=66), 60% with SAA (n=51), and 42% with MDS (n=29). With AML, it is clearly shown that the disease state at UBMT influences the outcome very much (Figure 9). As shown in Table 1, the incidence of grade >II acute graft-versus-host disease (AGVHD) is 2.3 fold as high as that of the HLA-identical sibling BMT. These values look the same as were expected (2,3), but it is still too early to give a conclusion to UBMT in Japan.

Problems and Future Directions

According to a report from Bone Marrow Donor Worldwide, more than 1,200,000 donors have been registered in 28 donor banks in 26 countries as of 1993 However, each bank has still few donors of oriental origin. Therefore the Japanese donor registry will be useful for the international donor recruitment as mentioned already. We hope that the size of registered donor pool will become bigger and bigger. However, we should remind that there still remain many essential problems to be solved in BMT, which is more serious in UBMT They include the low curable rate, the unguaranteed donor safety, the high incidence of severe GVHD, the long waiting time, and the insufficient number of specialists. As far as we have these problems, we should remind that the UBMT is still at the investigational stage. In other words, we should not be proud of the high increasing rate of UBMT number. Therefore, we urgently need Bone Marrow Harvesting/Transplantation Centers with both clinical research facilities and BMT education programmes for training the specialists.

Acknowledgement

The author thanks all JMDF and JRC staff members for their providing the data.

References

1. The Central Coordination Committee of the Japan Marrow Donor Foundation: *Bone Marrow Transplantation* 13: 699, 1994

2. Okamoto S, Asano S, Shibata H, et al: *Bone Marrow Transplantation* 13: 741, 1994

3. Morishima Y, Kodera Y, Hirabayashi N, et al: *Bone Marrow Transplantation* 15: 235, 1995

Table 1 Incidence of AGVH in UBMT

	Donor	Grade of AGVHD (%) I II III IV >II
IMSUT (n=86)	HLA-identical Sibling	45 10 7 2 20
JMDP (n=314)	Unrelated	29 22 14 11 46

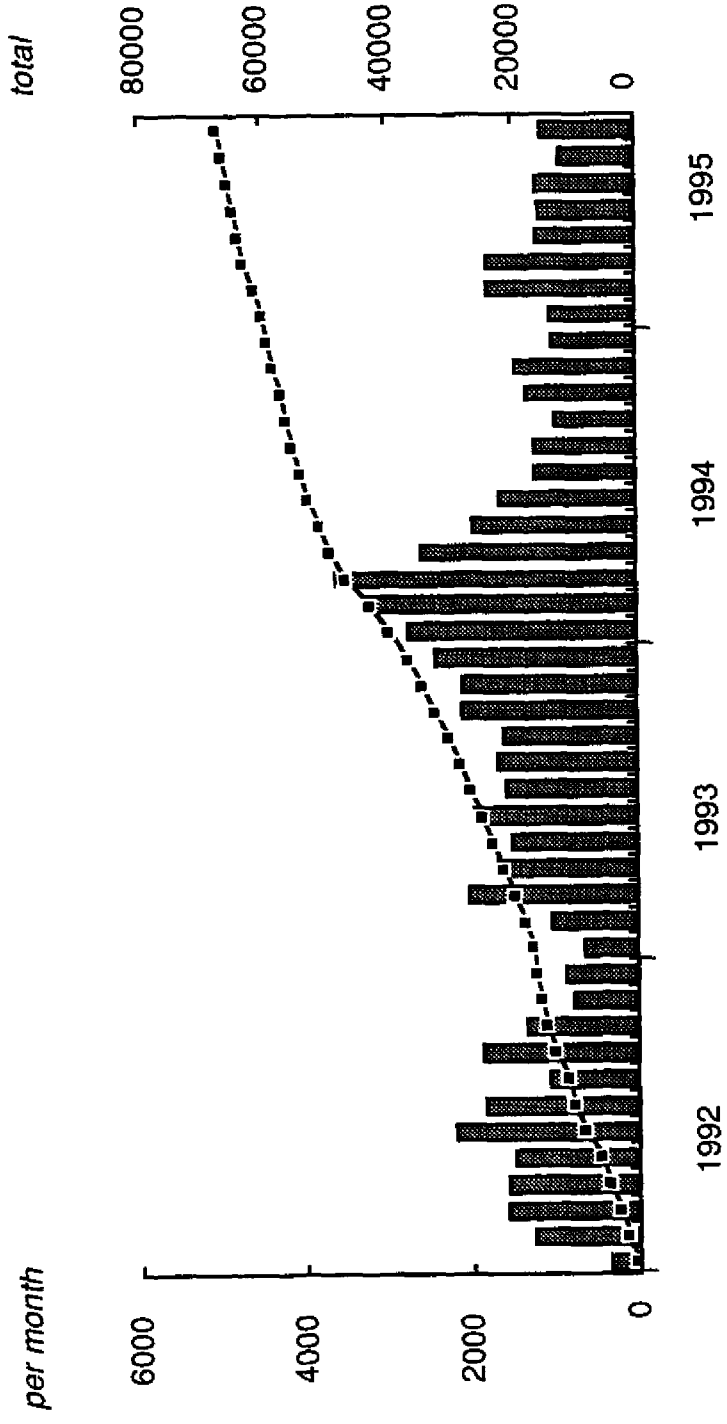


Fig. 1 Change in Number of Volunteer Donors Registered (column; number per month, dotted line; accumulated number)

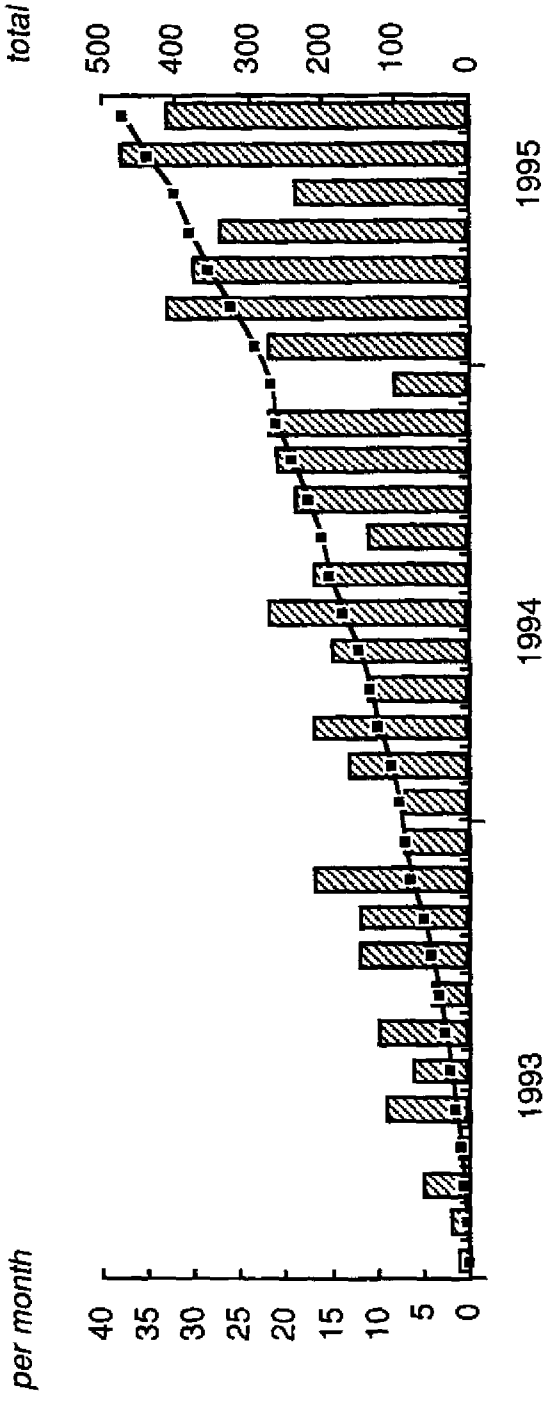


Fig. 2 Change in Number of patients received UBMT (column; number per month, dotted line; accumulated number)

Figure 3. Disease Distribution f UBMT (n=498) as of August 1995

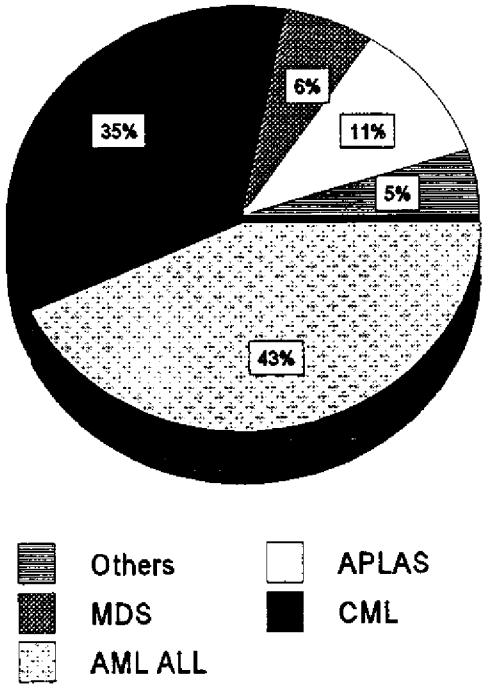
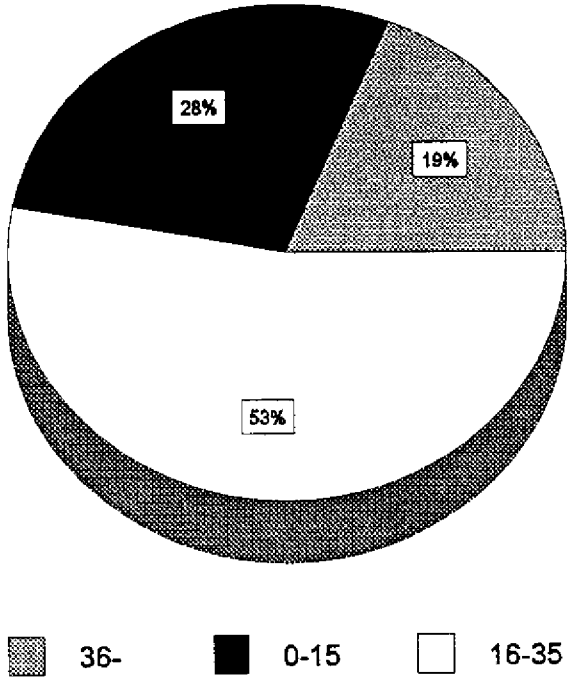


Fig. 4 Age Distribution of UBMT (n=498) as of August 1995



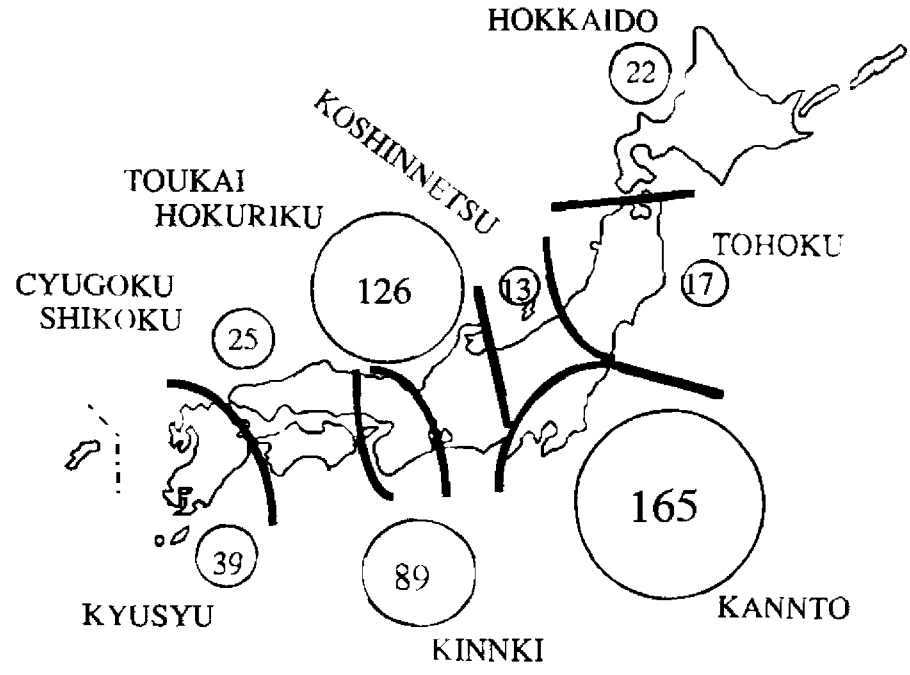


Fig. 5 Regional Difference of UBMT Patient Number (n=498) as of August 1995

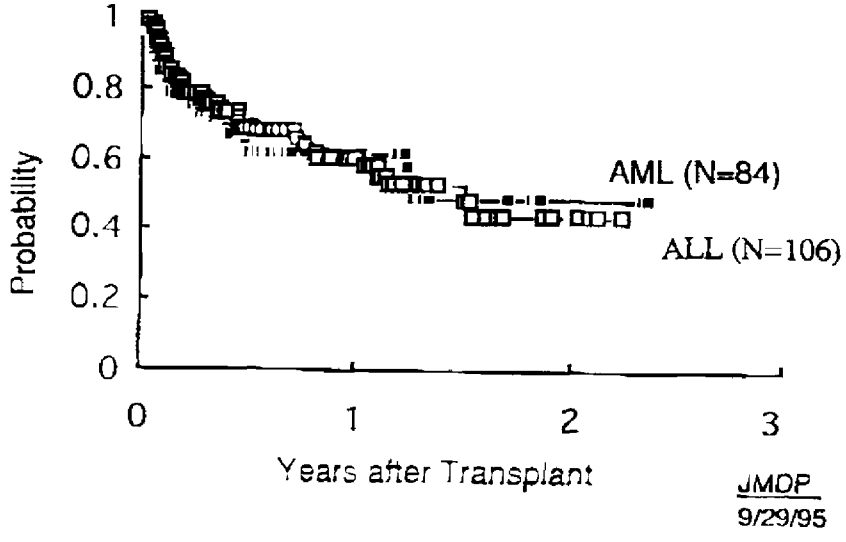


Fig. 6 Survival Probability of Acute Leukemia Patients Receiving UBMT

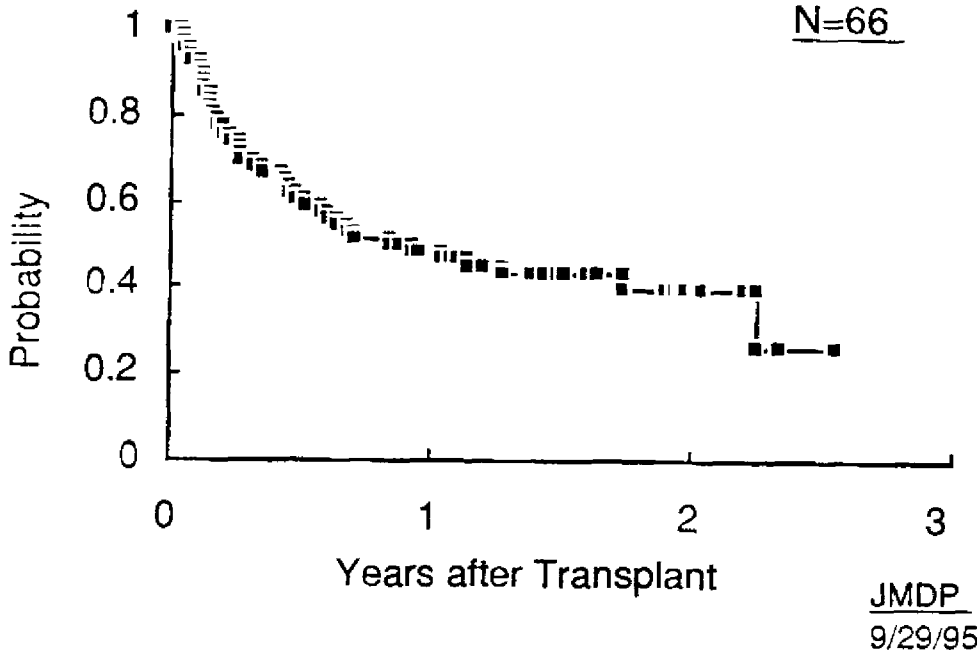


Fig. 7 Survival Probability of CML Patients Receiving UBMT

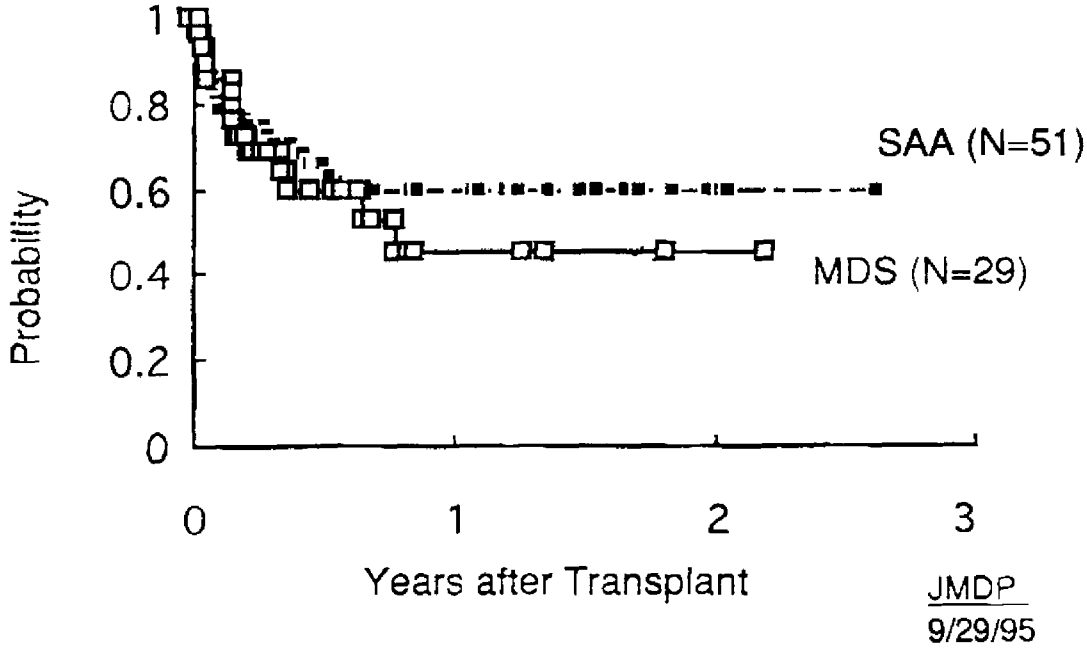


Fig. 8 Survival Probability of SAA and MDS Patients Receiving UBMT

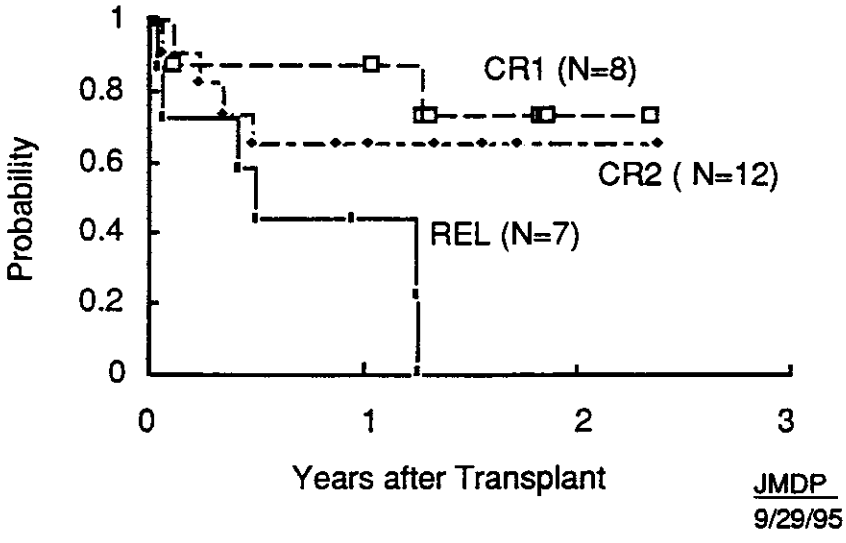


Fig. 9 Survival Probability Difference among the disease states at UBMT for AML

3. Iodine Prophylaxis for the Accident of Nuclear Power Stations

Shigenobu Nagataki, M.D.
Dean, Nagasaki University School of Medicine

Tomoko Nishikawa, M.D., Research Associate
First Department of Internal Medicine
Nagasaki University School of Medicine
Nagasaki, Japan

Introduction

The explosions of nuclear weapons or accidents at nuclear power stations can affect the thyroid gland, and radiation-induced thyroid diseases are due to exposure to radiation at the time of explosion or to radioactive fallout (external radiation) and exposure to radioactive iodine that accumulates within the thyroid (internal radiation).

Reports on radiation-induced thyroid diseases

1. Atomic bomb survivors (external radiation)

A significant dose response relationship was observed in 1) thyroid cancer, 2) thyroid adenoma, 3) thyroid nodules without histological diagnosis, and 4) autoimmune hypothyroidism. The time of confirmation was at least several years after the explosion (1,2).

2. Medical external radiation

Thyroid cancer was induced in children by medical external radiation for enlarged thymus (3), tinea capitis (4,5), skin hemangioma (6,7) and cancer therapy. Mean radiation doses were from 0 06 to 1.4 Gy except cancer therapy

3. Radioactive fallout

Marshall Islands. In Marshall Islanders, radiation-exposure resulted from both internal and external sources, and thyroid cancer, thyroid nodule and thyroid atrophy were reported to be due to the radioactive fallout. However, it is not clear whether these diseases are due to external radiation from fallout, short-lived or long-lived radioactive iodine (8)

Chernobyl. It is confirmed that there are many children with thyroid cancer in Republic of Belarus, Ukraine and Russian Federation. The incidence of thyroid cancer increased after the Chernobyl accident in the three Republics. It is very likely that the cause of thyroid cancer is the radioactive fallout. However, as in Marshall Islands, it is not known yet which radioactivity is the cause of thyroid cancer (9).

4. Medical use of I^{131}

Therapeutic dose. Therapeutic doses of I^{131} clearly induce hypothyroidism within several weeks after the irradiation. However, there are no reports that I^{131} induced thyroid cancer at least in humans (10).

Diagnostic dose Several reports showed that no significant thyroid diseases were induced by the diagnostic doses of I^{131}(11)

Thyroid and medical emergency

A very large dose of radiation (both external and internal) can induce hypothyroidism within several weeks. However, this type of radiation exposure was reported only in the case of the medical use of radiation.

Thyroid cancer can be induced by relatively low dose of external radiation (atomic bomb survivors and medical treatment). Thyroid cancer can also be induced by the radioactive fallout which will cause external radiation exposure and contain short- and long-lived radioactive iodines but there are no reports that I^{131} induces thyroid cancer. Thyroid cancer was confirmed at least several years after the exposure

Thyroid and medical preparedness

There are no effective treatments to prevent thyroid diseases after irradiation

Therefore, it is important to prevent a) external radiation, b) radiation from inhalation, especially short-lived radioactive iodine, and c) oral intake of radioactive iodine.

Prevention of thyroid glands from internal radiation by stable iodide (Iodine Prophylaxis) is widely employed and many international and national organizations have very similar recommendations (Table 1). However, in order to discuss iodine prophylaxis for radiation emergency, it is essential to define various conditions at the time of emergency. In this presentation, iodine prophylaxis for the accident of nuclear power stations in Japan is picked up as an example, and the updated recommendation will be discussed.

Iodine prophylaxis for the accident of nuclear power stations in Japan

1 The condition at the time of emergency

In Japan, 1) the first information about the accident can be delivered from the headquarter 30 hours before the actual release of radioactive materials from the reactor, 2) the area of radioactive fallout is less than 10 kilometers from the nuclear power station regardless of the climates and 3) very precise information can be broadcasted from the headquarter 30 hours before the radioactive fallout. Therefore, it is possible 1) to evacuate many inhabitants from the fallout area before the actual fallout of radioactive materials, 2) to prevent completely the oral intake of radioactive materials and therefore, the main source of radioactivity may be from inhalation, and 3) to start iodine prophylaxis before the release of radioactive iodine.

2. Newborns, children and pregnant women

In these conditions, newborns, children and pregnant women who are very sensitive to radioactive iodine and on whom side effects of stable iodine are not confirmed yet, have to be evacuated without iodine prophylaxis before the radioactive fallout (2,12-17).

3. Patients with thyroid diseases

Patients with thyroid disease or with history of thyroid disease may have side effects of iodine prophylaxis (18). Iodide-induced thyrotoxicosis, blocking the effects of anti-thyroid drugs in Graves' disease and iodide-induced hypothyroidism in chronic thyroiditis are very common but are not fatal and reversible. They have to be evacuated, if possible, before the release of radioactive materials without iodine prophylaxis

4. Subjects with a history of allergy to iodide

Side effects of stable iodide administration include anaphylaxis and allergic reactions which can be fatal

They have to be evacuated also without iodine prophylaxis.

5. Healthy adult subjects in the fallout area after the release of radioactive materials

1) As for stable iodine prophylaxis, only a single dose within several hours before the release of radioactive materials may be enough to prevent radioiodine uptake to thyroid glands (Fig.1)(19), since it is possible to evacuate almost all subjects from the contaminated area within 24 hours. The question on the dose of iodide; 30, 50, or 100 mg is more psychological and political rather than scientific issue (Fig.2)(20).

2) Since radioactive iodine may be absorbed mainly by inhalation at least in the above condition and radioactive iodine immediately after the accident may include various short-lived isotopes which are more carcinogenic than I^{131}, prevention of contaminated air using the mask with water or charcoal and prevention of external radiation are as important as stable iodine prophylaxis.

6. Workers who have to work in the fallout area

Workers who have to work in the contaminated area, 100 mg of KI once every 24 hours or 50 mg of KI once every 12 hours has to be given for as long as they stay in the contaminated area, assuming that patients with thyroid disease or allergic to iodide are evacuated. However, it should be noted that 30 mg of KI for 4 weeks decreased serum thyroxine levels and increased serum TSH concentrations and the size of thyroid glands (Fig.3)(21). In addition to iodine prophylaxis, it is important to prevent contaminated air and external radiation to the thyroid at the early period of the accident.

Dietary intake of iodide in Japan

The diet customarily includes large quantities of foods rich in iodine and the average daily intake of iodine is 1 to 3 mg. However, the frequency of ingestion of iodine-rich foods vary greatly from 0.1 to 20 mg of iodide per day. Although average intake of iodide is very high, dietary intake of iodide can not be the iodine prophylaxis (22).

Summary

A very large dose of radiation (both external and internal) can induce hypothyroidism within several weeks. However, this type of radiation exposure was reported only in the case of the medical irradiation. Thyroid cancer can be induced by the radioactive fallout which will cause external irradiation and short- and long-lived radioactive iodines, but in Marshall Islands and Chernobyl there are no reports which showed that I^{131} induced thyroid cancer. Thyroid cancer was confirmed at least several years after the exposure.

There are no effective treatments to prevent thyroid diseases after irradiation. Therefore, it is important to prevent a) external irradiation, b) irradiation from inhalation, especially short-lived radioactive iodine, and c) oral intake of radioactive iodine.

In the accident of nuclear power stations in Japan, a) the first information about the accident can be delivered from the headquarter 30 hours before the actual release of radioactive materials from the reactor, b) the area of radioactive fallout is less than 10 kilometers from the nuclear power station regardless of the climate and c) very precise information can be broadcasted from the headquarter 30 hours before the radioactive fallout. In this connection, the following are recommended as the medical preparedness to radiation emergency.

Subjects	Medical preparedness
Population at risk - neonates, children and pregnant women - patients with thyroid diseases subjects with a history of allergy to iodine	Evacuate without iodine prophylaxis
Population not at particular risk - healthy adults	Give a single dose of 30, 50 or 100 mg of KI before the release of radioactive materials and evacuate them within 24 hours.
- workers in the fallout area	Give 50 or 100 mg of KI once every 24 hours as long as they stay in the contaminated area Prevent from external radiation and from radiation by inhalation

Acknowledgement

The authors would like to express our sincere thanks to members of working group for Iodine Prophylaxis, supported by Nuclear Safety Research Association, for their very useful suggestions on the accident of nuclear power stations in Japan.

Bibliographical References

1. Akiba S, et al. Thyroid cancer incidence among atomic bomb survivors, 1958-79. *RERF Technical Report* 5-91, Japan, 1991

2. Nagataki S, et al. Thyroid disease among atomic bomb survivors in Nagasaki. *The Journal of American Medical Association* 272 (5): 364-370, 1994

3. Shore RE, et al. Thyroid cancer among persons given X-ray treatment in infancy for an enlarged thymus gland. *American Journal Epidemiology* 137 (10): 1068-1080, 1993

4. Ron E, et al. Thyroid neoplasia following low dose radiation in childhood. *Radiation Research* 120: 516-531, 1989

5. Shore RE, et al. Carcinogenic effects of radiation on the human thyroid gland. *Radiation Carcinogenesis*, New York, Elsevier, 1986

6. Furst CJ, et al. Cancer incidence after radiotherapy for skin hemangioma: A retrospective cohort study in Sweden. *Journal of the National Cancer Institute* 80 (17): 1387-1392, 1988

7. Lundell M, et al. Thyroid cancer after radiotherapy for skin hemangioma in infancy. *Radiation Research* 140: 334-339, 1994

8. Robbins J, et al. Radiation effects in the Marshall Islands. *Radiation and Thyroid*, Amsterdam, Excepta Medica, 1989

9. Nagataki S, et al. Symposium on Chernobyl: Update and future, Amsterdam, Excepta Medica, 1989

10. Holm L, et al. Cancer risk after iodine-131 therapy for hyperthyroidism. *Journal of the National Cancer Institute* 83 (15): 1072-1077, 1991

11. Holm L, et al. Thyroid cancer after diagnostic doses of iodine-131: A retrospective cohort study. *Journal of the National Cancer Institute* 80: 1132-1138, 1988

12. Evans TC, et al. Radioiodine uptake studies of the human fetal thyroid. *Journal of Nuclear Medicine* 8:157-165, 1967

13. Fisher DA, et al. Thyroid development and disorders in the newborn. *New England Journal of Medicine* 304: 702-712, 1981

14. Sternthal E, et al. Suppression of thyroid radioiodine uptake by various doses of stable iodine. *New England Journal of Medicine* 303: 1083-1088, 1980

15. Hodges RE, et al. The accumulation of radioactive iodine by human fetal thyroids. *Journal of Clinical Endocrinology and Metabolism* 15: 661-667, 1955

16. Delange F, et al. Transient disorders of thyroid function and regulation in preterm infants. *Pediatric Thyroidology,* Karger, Basel, 1985

17. Van Middlesworth L, et al. Radioactive iodine uptake of normal newborn infants. *American Journal of Diseases in Children* 88: 439-442, 1954

18. Nauman J, et al. Iodine prophylaxis in Poland after the Chernobyl reactor accidents: Benefits and risks. *The American Journal of Medicine* 94:524-532, 1993

19. Becker DV, et al. Reactor accidents public health strategies and their medical implications. *The Journal of American Medical Association* 258 (5): 629-655, 1987

20. Sternthal E, et al. Suppression of thyroid radioiodine uptake by various doses of stable iodine. *New England Journal of Medicine* 303 (19): 1083-1088, 1980

21. Namba H, et al. Evidence of thyroid volume increase in normal subjects receiving excess iodine. *Journal of Clinical Endocrinology and Metabolism* 76 (3): 605-608, 1993

22. Nagataki S, et al. Status of iodine nutrition in Japan. *Iodine Deficiency in Europe,* New York, Plenum Press, 1993

Table 1

RECOMMENDATION FOR DOSE OF STABLE IODINE

WHO			IAEA		ICRP		USAFDA		JAPAN	
dose of stable iodine	adult 3-12 y	100mg 50mg	adult children less than	100mg 100mg	adult 3-12y	100mg 50mg	adult children	100mg	adult children	100mg
	1-3y newborns	25mg 12.5mg			3y>	25mg	1y< 1y>	100mg 50mg	1y< 1y>	100mg 50mg

Figure 1. Effect of time of administration of potassium iodine on its protective effect in blocking thyroid uptake (19)

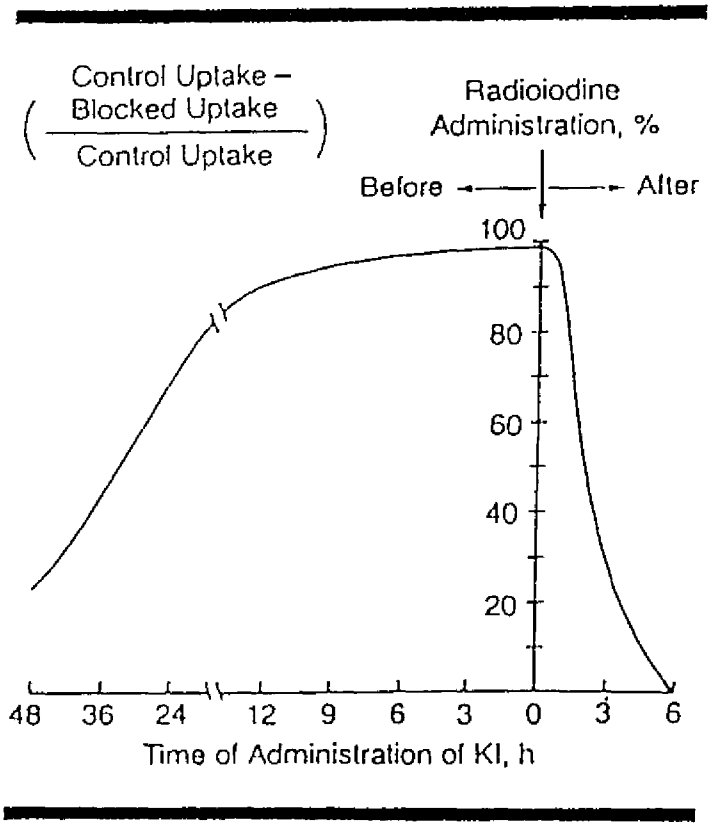
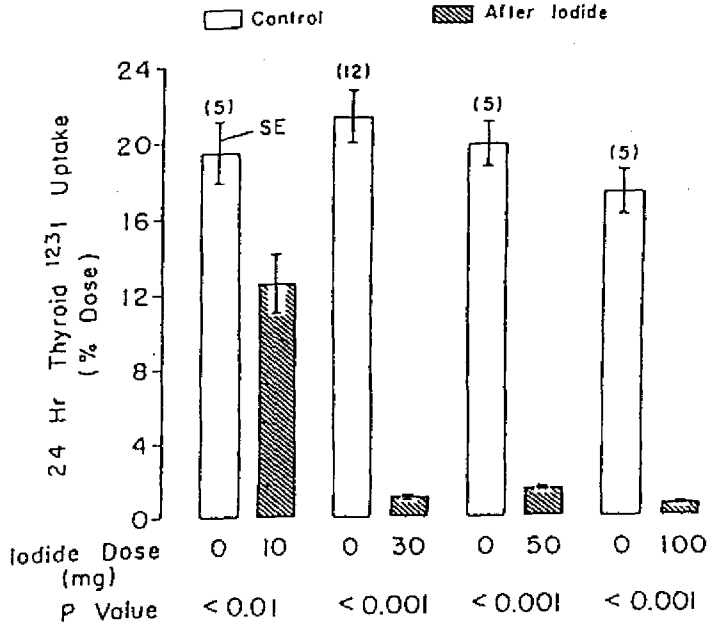


Figure 2. Effect of different single doses of iodine on 24 hour thyroid uptake of ^{123}I (20)



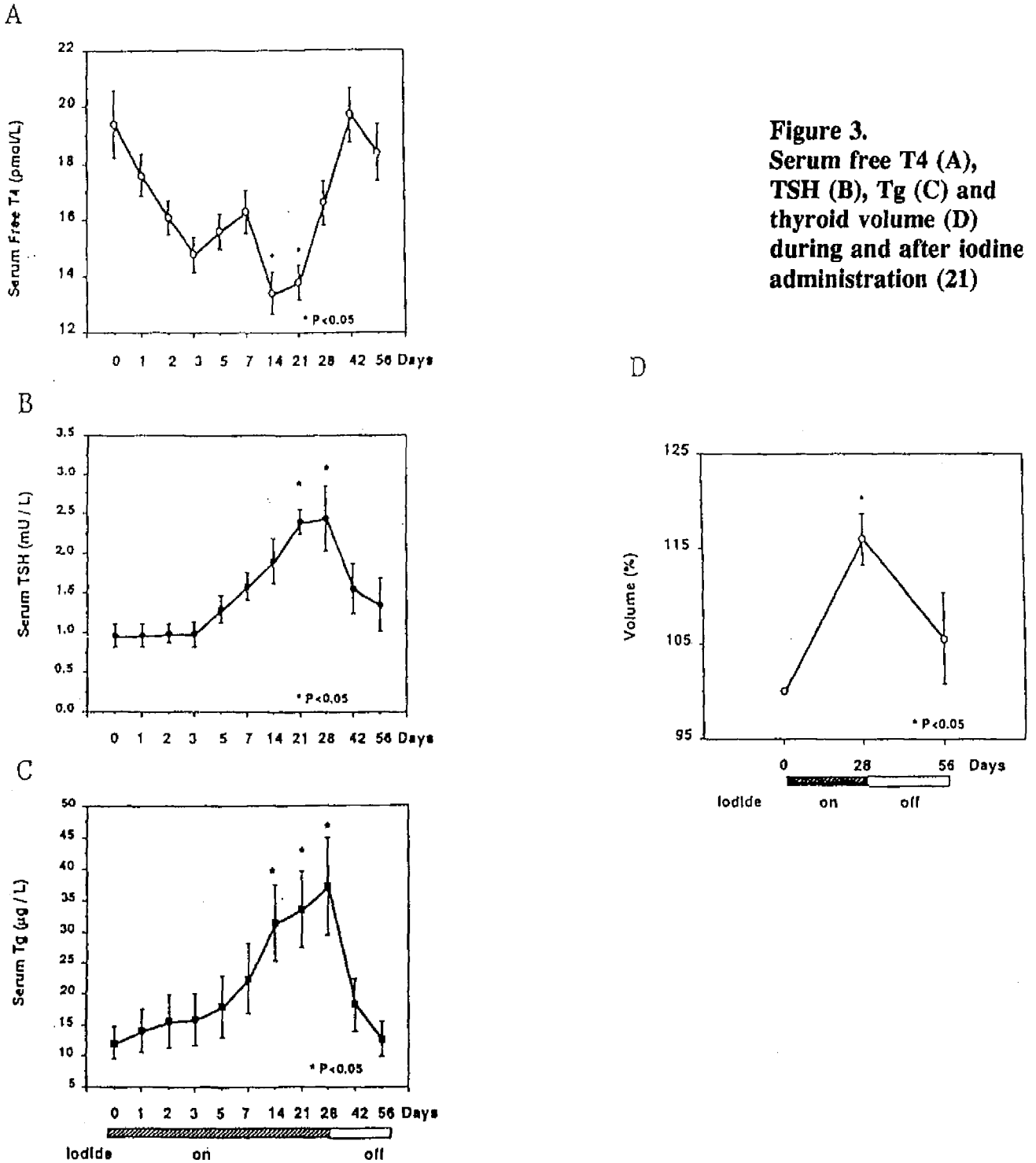


Figure 3.
Serum free T4 (A), TSH (B), Tg (C) and thyroid volume (D) during and after iodine administration (21)

4. Chelation Therapy in Japan: A Report Based on 25-Year Use of CaEDTA in Occupational Medicine

Shunichi Araki, M.D., D.M.Sc., MSc.
Fumihiro Sata, M.D., Katsuyuki Murata, M D., D.M.Sc.
Department of Public Health, Faculty of Medicine, University of Tokyo
Tokyo, Japan

Introduction

Calcium disodium ethylenediamine tetraacetate (CaNa2EDTA or CaEDTA) is the most common chelating agent used in man, primarily to treat lead poisoning. It can also be used to chelate zinc, manganese, cadmium, copper, chromium and nickel And, it has some effectiveness for transuranium metals such as plutonium and americium. CaEDTA is easily available to physicians from a pharmaceutical company in Japan. We have administered this agent by intravenous infusion for diagnosis and treatment of lead poisoning for 25 years.

On the other hand, calcium trisodium diethylenetriamine pentaacetate (CaNa3DTPA or CaDTPA) has been found to be more effective for plutonium, americium and other radionuclides. However, in Japan, neither CaDTPA nor ZnDTPA has been available for clinical use.

In this report, following a short review on DTPA and other chelating agents, major findings in our past studies with CaEDTA in metal workers are summarized. The topics are as follows: (1) Mobilization yield of heavy metals into urine by CaEDTA in healthy humans and metal workers, (2) relations of mobilization yield of heavy metals in urine to plasma and erythrocyte metal concentrations and exposure indicators, (3) changes in lead, zinc and copper in plasma, erythrocytes and urine after intravenous infusion of CaEDTA in relation to δ-aminolevulinic acid dehydratase (ALAD) activity; (4) assessment of the whole body burden of chelatable lead, zinc and copper, (5) diminution rates of blood lead and mobilization yield of lead in urine by CaEDTA, and (6) adverse effects of CaEDTA.

A Short Review on DTPA and Other Chelating Agents

(Slide 1): This short review is indebted to "Medical Handling of Accidentally Exposed Individuals" published by International Atomic Energy Agency, Vienna, in 1988.

(Slide 2): A number of chemical compounds enhance the elimination of metals from the body by chelation. The chelated metals can be excreted readily by the kidney. A properly selected and administered chelating drug will enhance the excretion of some radionuclides. Therapy with a chelating agent is most effective when it is begun immediately after exposure.

CaEDTA is used primarily to treat lead poisoning. It has some effectiveness for plutonium, americium and other transuranium metals, but CaDTPA has been found to be more effective for these radionuclides.

CaEDTA might be nephrotoxic and must be used with extreme caution in patients with preexisting renal disease.

(Slide 3): The powerful chelating agent DTPA is more effective than CaEDTA in removing transuranium metals (i.e., plutonium, americium, curium, californium, and neptunium), the rare earths (i.e , cerium, yttrium, lanthanum, promethium and scandium), and some transition metals (e.g., zirconium and niobium). Two forms of DTPA are available for clinical use of treatment of plutonium and americium exposures, the calcium salt (CaDTPA) and the zinc salt (ZnDTPA).

CaDTPA also binds trace metals present in the body, such as zinc and manganese. It is the reduction in

these two trace metals that probably accounts for the toxicity to high doses in animal experiments.

ZnDTPA is less toxic than CaDTPA; therefore, ZnDTPA is advantageous to use for longer-term treatments, and especially for fractionated treatments. Also, no serious toxicity in man has been reported as a result of using CaDTPA or ZnDTPA in recommended doses.

CaDTPA is more effective than ZnDTPA in rats when given promptly after exposure to ^{239}Pu, ^{252}Cf, or ^{241}Am. This finding led to the general recommendation that CaDTPA be used during the first 24 to 48 hr after exposure and then that ZnDTPA be used for continuing treatments.

(Slide 4): The effectiveness of DTPA in enhancing the excretion of plutonium is markedly affected by the chemical form of the plutonium. For both wounds and inhaled particles, the uptake of relatively insoluble plutonium compounds, such as plutonium oxide, into the circulation occurs over many days and weeks. DTPA is not effective in these cases because of the small amount of plutonium present soon after exposure in the blood or intracellular fluids. Soluble compounds, such as plutonium nitrate, have relatively rapid uptake and translocation, and so the plutonium is more available early after exposure for chelation. Data from persons treated with CaDTPA soon after exposure (on the first day) indicate that about 60 to 70% of the soluble forms of plutonium are removed.

Both CaDTPA and ZnDTPA are available as an investigational new drug (IND) in the United States, and can be obtained through the Radiation Emergency Assistance Centre and Training Site, Oak Ridge, Tennessee. They may also be readily available from pharmacies, as is CaDTPA in Germany. These drugs have been administered by both intravenous injection and aerosol inhalation.

In cases of uranium incorporation, chelating agents should not be given since the kidney may then be subjected to uranium overload. Treatment to remove uranium intakes is not particularly successful, but sodium bicarbonate in saline may be given by slow intravenous infusion.

The recommended dose for DTPA is 1 g per day. The dose should not be fractionated, i.e., given in multiple doses per day. The intravenous administration of 1 g DTPA in 250 ml normal saline or 5% glucose in water over 30 minutes has been the usual procedure. An alternate procedure, 1 g diluted in 10 or 20 ml normal saline and injected intravenously by syringe over five min, is preferred by some physicians. In either case, care should be taken to avoid extravasation from the vein. Aerosol administration is done with 1 g CaDTPA placed in a nebulizer and the contents inhaled over 15 to 20 min Because of its metallic taste, ZnDTPA is less suited than CaDTPA for aerosol administration It is prudent not to use the inhalation route in persons with preexisting pulmonary disease. The drug is also contraindicated if significant leucopenia, thrombocytopenia, or kidney dysfunction exists. Clinical urinalysis should be normal prior to each treatment. A treatment protocol and follow-up reports are required under the terms of the IND (i.e., investigational new drug) agreement.

(Slide 5): There is evidence that the water soluble derivative DMPS (dimercapto propan sulphonate) available as Dimaval in many countries is more effective and less toxic than BAL (British Anti-Lewisite, i.e., dimercaprol). Its use has been recommended for treatment of mercury, lead or polonium incorporation

Penicillamine, an amino acid derived from the degradation of penicillin, chelates with copper, iron, mercury, lead, gold, and possibly other heavy metals. It is superior to dimercaprol and CaEDTA for the removal of copper.

Deferoxamine (DFOA) has been used effectively in the treatment of iron storage diseases and acute iron poisoning If given promptly, DFOA surpasses CaDTPA in the enhancement of excretion of plutonium (IV) compounds. Its effectiveness declines rapidly, which makes its clinical use for this purpose questionable The combination of DFOA and CaDTPA yields better results than either drug separately.

Studies with CaEDTA by Us

1. Mobilization yield of heavy metals into urine by CaEDTA

(Slide 6): We measured mobilization yield of seven heavy metals into urine by CaEDTA in 20 metal workers exposed to lead, zinc and copper. CaEDTA was administered in a dosage of 20 mg per kg body weight by intravenous infusion.

(Slide 7): Blood lead (BPb) concentration in these workers ranged from 22 to 59 (mean 38) μg/dl. This slide shows the mobilization yields of Pb, Hg, Cd, Zn, Cu, Mn and Cr. The mobilization yield was on average 13 times the background excretion for lead, 11 times for zinc, 3.8 times for manganese, 3.4 times for cadmium, 1.3 times for copper, and 1.1 times for chromium; no significant increase was found for mercury.

(Slide 8): In 1973, we studied 45 healthy adults without occupational exposure to lead.

(Slide 9): In males aged 19-59 (mean 36), the mobilization yield of lead (MPb) ranged from 43 to 172 (mean 95) μg/24 hrs. In females aged 19-50 (mean 31), it was 22-123 (mean 56) μg/ 24 hrs.

2. Relations of mobilization yield of heavy metals in urine to the plasma and erythrocyte concentrations and exposure indicators

(Slide 10): We examined relationships between mobilization yield of 7 heavy metals and various exposure indicators. MPb was significantly correlated with the whole blood and erythrocyte concentrations and spontaneous urinary excretion of lead but not with its plasma concentration.

(Slide 11): Similarly, the mobilization yield of cadmium (MCd) was significantly correlated with its erythrocyte concentration.

(Slide 12): MPb was also significantly correlated with ALAD and urinary coproporphyrin excretion.

3. Changes in heavy metals in plasma, erythrocytes and urine after CaEDTA administration

(Slide 13): We measured concentrations of lead and zinc in plasma, erythrocytes, whole blood, and urine in seven lead workers after CaEDTA was administered by intravenous infusion for 1 hr.

(Slide 14): The mobilization yields of lead and zinc were the highest during the period between 1 and 2 hr and between 0 and 1 hr, respectively, after the infusion was started.

(Slide 15): The plasma lead concentration (PPb) was also highest during the period between 1 and 2 hrs after the start of CaEDTA infusion. In contrast, plasma zinc concentration (PZn) fell rapidly following CaEDTA infusion; the decline was followed by a gradual rise in the zinc concentration in erythrocytes (EZn) without alteration in the zinc in whole blood.

(Slide 16): ALAD activity in erythrocytes gradually increased for 5 hr following CaEDTA infusion.

These observations suggested that (1) MPb is mostly mobilized not from plasma but from other body organs after CaEDTA administration, followed by a transient but marked increase in plasma lead; (2) on the other hand, MZn is mobilized mostly from plasma during the first several hours following the start of CaEDTA infusion, and the fall in PZn concentration following infusion is compensated first by a rise in EZn concentration and then by an immediate redistribution of zinc in other organs to the blood; and (3) lead-inhibited ALAD activity is reactivated by the increased EZn during and shortly after CaEDTA infusion.

In addition, we also examined the concentrations of copper in plasma, erythrocyte and urine and ALAD activity in erythrocyte in ten male gun metal founders; a peak in the mobilization of copper during the time period between 2 and 4 hrs after CaEDTA infusion was found.

4. Relationships between the mobilization yield of lead in urine and the body burden of chelatable lead

(Slide 17): We have introduced a hypothetical model to estimate the whole body burden of chelatable lead from MPb by CaEDTA The study is based on two assumptions: (1) the proportion of MPb to the body burden of chelatable lead in lead workers is constant regardless of the size of the chelatable lead pair as disclosed by Teisinger et al in rabbits, and (2) non-chelatable lead is converted to chelatable lead in negligibly small quantities during the 24 hours after the CaEDTA injection

(Slide 18): It was estimated that, on average, 14% of the whole body burden of chelatable lead was mobilized into the urine during the 24 hours after an injection of 20 mg CaEDTA per kg body weight. The body burden of chelatable lead ranged from 0.8 to 24.9 mg (mean 7.7 mg) in lead workers with blood lead concentrations of 6-60 (mean 29) µg/dl.

(Slide 19): There were linear relationships between blood lead concentrations and body burden of chelatable lead on a log scale

5. Diminution rates of blood lead and mobilization yield of lead into urine by CaEDTA

(Slide 20): We examined the diminution rates of blood lead and mobilization of lead into urine by CaEDTA in two lead workers, to whom CaEDTA 20 mg/kg was administered weekly for 3.5 years after termination of occupational exposure.

(Slide 21): The diminution half-lives for lead in blood and urinary lead mobilized by CaEDTA were 4.8 and 3.3 years respectively for one subject following 28 years exposure and 3 3 and 2.0 years respectively for another subject following 26 years exposure. The difference in the diminution rate between lead in blood and lead mobilized by CaEDTA was significant in one subject. This was assumed to be the first report of long-term observation on the diminution rate of mobilization yield of lead in lead workers.

6. Side-effects

Hundreds of our diagnostic and therapeutic uses of CaEDTA have failed to gather any evidence that single or periodic uses of CaEDTA with the ordinary dose, i.e., less than 2 g CaEDTA in 250 ml of 5% glucose solution, are hazardous to patients with normal renal function. We have not found even transient proteinuria in all workers examined by us.

SAFETY SERIES No. 88

MEDICAL HANDLING OF ACCIDENTALLY EXPOSED INDIVIDUALS

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 1988

(Slide 1)

4.4.5. Chelating agents

A number of chemical compounds enhance the elimination of metals from the body by chelation, a process by which organic compounds (ligands) exchange less firmly bonded ions for other inorganic ions to form a relatively stable non-ionized ring complex. This soluble complex can be excreted readily by the kidney. A properly selected and administered chelating drug will enhance the excretion of some radionuclides and thus reduce their residence times in the body. Therapy with a chelating agent is most effective when it is begun immediately after exposure while the metallic ions are still in circulation and before their incorporation within cells or deposition in bone.

The calcium salt of ethylenediaminetetraacetic acid (*calcium edetate*, CaNa EDTA or CaEDTA) is the most common form of chelator used in man, primarily to treat lead poisoning. It can also be used to chelate zinc, copper, cadmium, chromium, manganese and nickel. It has some effectiveness for the transuranium metals, such as plutonium and americium, but $CaNa_3DTPA$ has been found to be more effective by an order of magnitude for those radionuclides.

The edetates are nephrotoxic and must be used with extreme caution in patients with preexisting renal disease. Transient bone marrow depression, mucocutaneous lesions, chills, fever, muscle cramps, and histamine-like reactions (sneezing, nasal congestion, and lacrimation) have also been described.

(Slide 2)

The powerful chelating agent diethylenetriaminepentaacetic acid (pentathamil, DTPA) is generally more effective in removing many of the heavy metal, multivalent radionuclides than CaEDTA. It is effective for the transuranium metals (plutonium, americium, curium, californium, and neptunium), the rare earths (cerium, yttrium, lanthanum, promethium and scandium), and some transition metals (zirconium and niobium). The clinical use of Ca- and ZnDTPA has been primarily for treatment of plutonium and americium exposures.

CaDTPA also binds trace metals present in the body, such as zinc and manganese. It is the reduction in these two trace metals that probably accounts for the toxicity to high doses in animal experiments.

The zinc salt of DTPA is less toxic than CaDTPA and therefore is advantageous to use for longer term treatments and especially for fractionated treatments.

CaDTPA is more effective than ZnDTPA in rats when given promptly after exposure to ^{239}Pu, ^{252}Cf, or ^{241}Am. This finding led to the general recommendation that CaDTPA be used during the first 24 to 48 hours after exposure and then that ZnDTPA be used for continuing treatments.

(Slide 3)

The effectiveness of DTPA in enhancing the excretion of plutonium is markedly affected by the chemical form of the plutonium. For both wounds and inhaled particles, the uptake of relatively insoluble plutonium compounds, such as plutonium oxide, into the circulation occurs over many days and weeks. DTPA is not effective in these cases because of the small amount of plutonium present soon after exposure in the blood or intracellular fluids. Soluble compounds, such as plutonium nitrate, have relatively rapid uptake and translocation, and so the plutonium is more available early after exposure for chelation. Data from persons treated with CaDTPA soon after exposure (on the first day) indicate that about 60 to 70% of the soluble forms of plutonium are removed.

Both CaDTPA and ZnDTPA are available as an investigational new drug in the United States and can be obtained through the Radiation Emergency Assistance Center and Training Site, Oak Ridge, Tennessee. They may also be readily available from pharmacies, as is CaDTPA in the Federal Republic of Germany. These drugs have been administered by both intravenous injection and aerosol inhalation.

In cases of uranium incorporation, chelating agents should not be given since the kidney may then be subjected to uranium overload. Treatment to remove uranium intakes is not particularly successful, but sodium bicarbonate in saline may be given by slow intravenous infusion.

(Slide 4)

There is evidence that the water soluble derivative DMPS (*dimercaptopropan-sulphonate*) available as *Dimaval* in many countries[2] is more effective and less toxic than BAL (British Anti-Lewisite, i.e. dimercaprol). Its use has been recommended for treatment of mercury, lead or polonium incorporation.

Penicillamine, an amino acid derived from the degradation of penicillin, chelates with copper, iron, mercury, lead, gold, and possibly other heavy metals. It is superior to dimercaprol and CaEDTA for the removal of copper.

Deferoxamine (DFOA) has been used effectively in the treatment of iron storage diseases and acute iron poisoning. If given promptly, DFOA surpasses CaDTPA in the enhancement of excretion of plutonium (IV) compounds. Its effectiveness declines rapidly, which makes its clinical use for this purpose questionable. The combination of DFOA and CaDTPA yields better results than either drug separately.

---

[2] Available, for example, in the People's Republic of China, the Federal Republic of Germany, Poland and the USSR.

(Slide 5)

British Journal of Industrial Medicine 1986; 43.636-641

Mobilisation of heavy metals into the urine by CaEDTA: relation to erythrocyte and plasma concentrations and exposure indicators

S ARAKI, H AONO, K. MURATA

From the Department of Public Health and Hygiene, Medical College of Oita, Hazama-machi, Oita 879-56, Japan

(Slide 6)

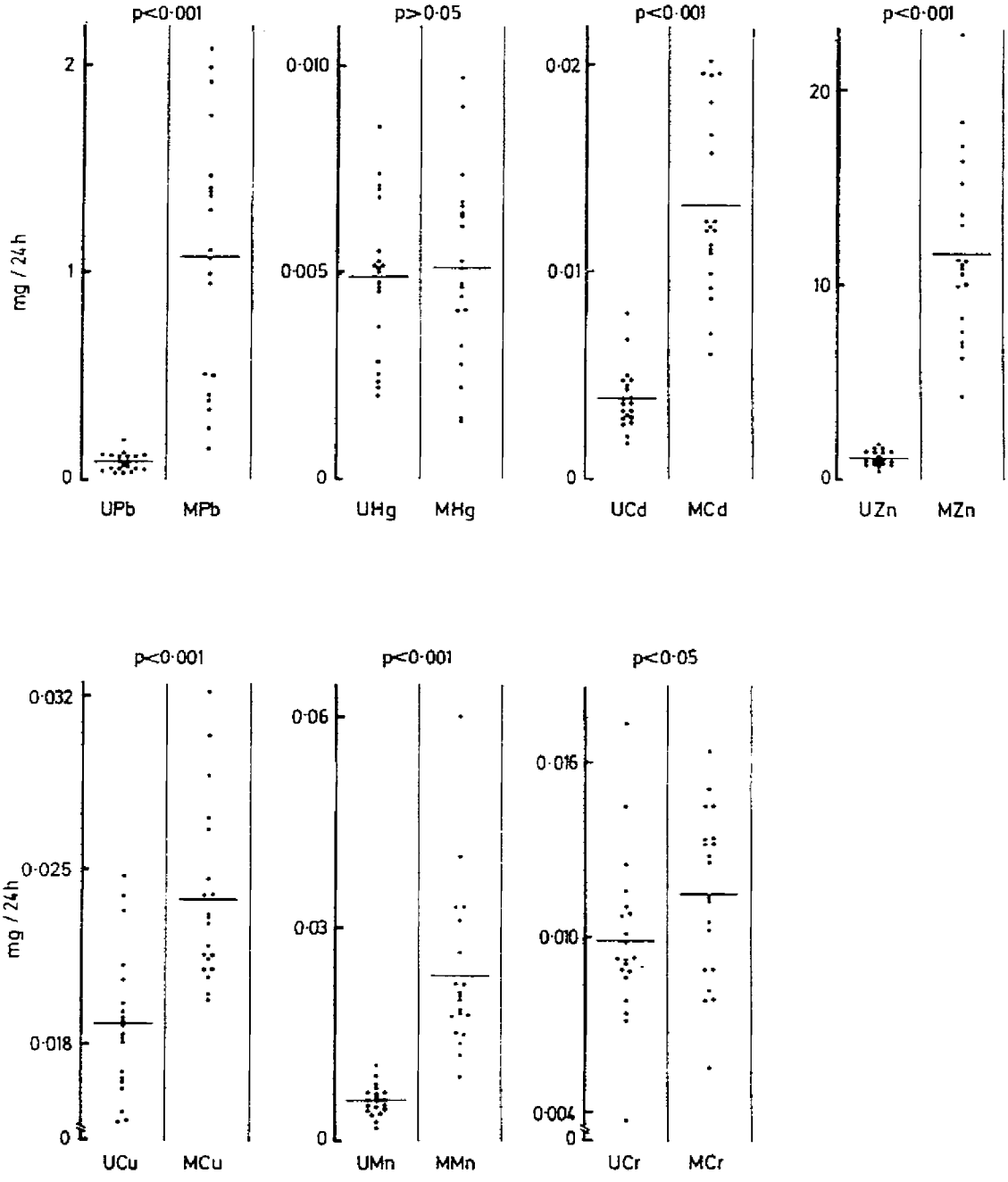


Fig 1 *Spontaneous urinary excretion of lead, mercury (total mercury), cadmium, zinc, copper, manganese, and chromium (UPb, UHg, UCd, UZn, UCu, UMn, and UCr) and their mobilisation yield in urine by CaEDTA (MPb, MHg, MCd, MZn, MCu, MMn, and MCr) in 20 subjects. Transverse line in each column shows mean value. In addition, no significant difference was found between urinary excretion of inorganic mercury before and after CaEDTA infusion ($p > 0·05$). 1 mg/24 h for lead, mercury, cadmium, zinc, copper, manganese, and chromium correspond to 4·8, 5·0, 8·9, 15, 16, 18, and 19 μmol/24 h, respectively.*

Ind. Health, 1973, 11, 203.

ON THE BEHAVIOUR OF "ACTIVE DEPOSIT OF LEAD (TEISINGER)" IN THE JAPANESE FREE FROM OCCUPATIONAL EXPOSURE TO LEAD

SHUNICHI ARAKI

Department of Public Health, Faculty of Medicine, University of Tokyo
Hongo, Bunkyo-ku, Tokyo

and

Department of Internal Medicine, Tokyo Rosai (Labour Accident) Hospital
Omori, Ota-ku, Tokyo

(Slide 8)

Table 2. Urinary excretion of lead before and after intravenous infusion of CaEDTA.

Lead in urine		Before CaEDTA	After CaEDTA	
		24-hr urine	2-hr urine	24-hr urine
A. Men (25 subjects)				
µg	Mean	20	12	95
	Range	<3—60	3—25	43—172
	95% region	1—56	3—26	37—172
	95% prediction interval	0—59	3—27	34—179
µg/l	Mean	13	40	53
	Range	<2—44	15—71, 120†	24—126
	95% region	0—39	9—86	16—104
	95% prediction interval	0—42	8—90	14—108
µg/l, SG 1.020	Mean	13	82	59
	Range	<2—35	22—157, 320††	18—105
	95% region	0—36	12—191	18—115
	95% prediction interval	0—38	10—202	16—120
µg/g, Cn	Mean	14	99	60
	Range	<1—53	41—173	22—108
	95% region	0—45	30—196	20—114
	95% prediction interval	0—48	26—205	18—118
µg/50 kg B.W.	Mean	16	10	75
	Range	<3—48	3—19	31—125
	95% region	0—45	4—17	31—132
	95% prediction interval	0—48	3—17	29—137
B. Women (20 subjects)				
µg	Mean	13	9	56
	Range	4—22	3—14	22—123
	95% region	4—25	2—15	16—110
	95% prediction interval	3—27	1—16	14—117
µg/l	Mean	12	41	43
	Range	4—20	10—64, 100†, 120†	13—72, 115†
	95% region	4—22	6—96	17—85
	95% prediction interval	3—23	5—103	10—91
µg/l, SG 1.020	Mean	11	75	49
	Range	4—24	31—113, 190†	19—117
	95% region	3—22	20—153	12—102
	95% prediction interval	2—23	17—162	9—109
µg/g, Cn	Mean	14	103	58
	Range	5—28	37—212	19—106
	95% region	3—30	30—204	19—113
	95% prediction interval	2—32	26—216	16—119
µg/50 kg B.W.	Mean	13	9	55
	Range	5—29	3—16	20—123
	95% region	3—28	2—18	17—107
	95% prediction interval	2—29	2—19	14—114

A dagger (†) indicates statistical significance at 5 per cent level by Smirnoff's test; a double dagger (††), 1 per cent level.

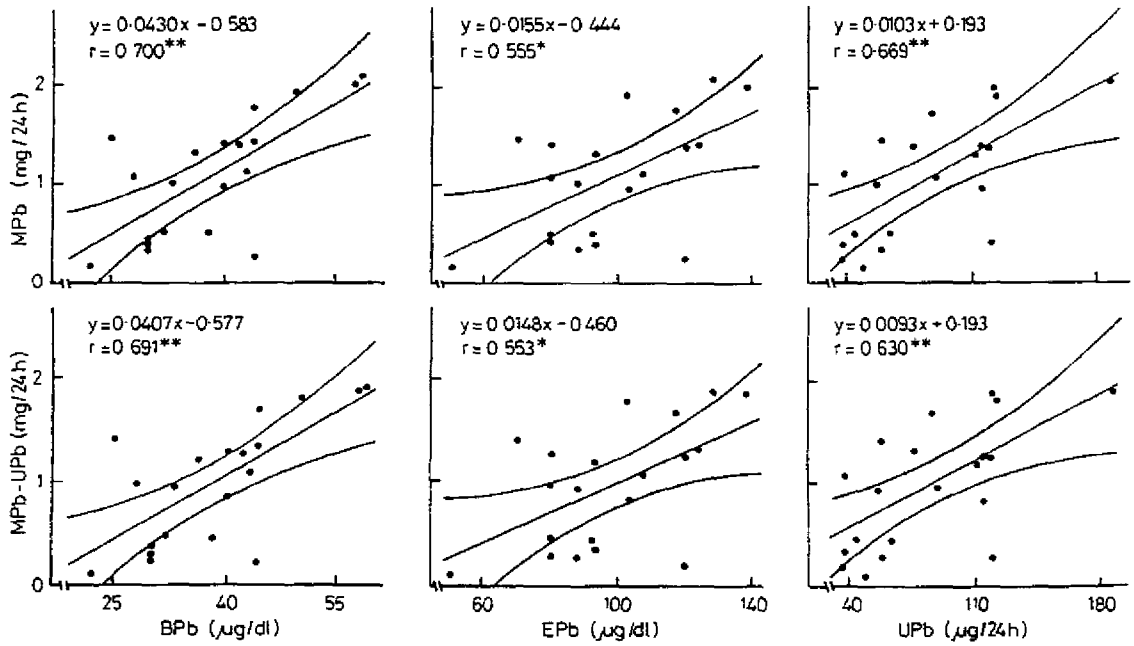


Fig 2 *Correlations of mobilisation yield of lead in urine by CaEDTA (MPb) and MPb minus spontaneous urinary excretion of lead (UPb) with its whole blood and erythrocyte concentrations (BPb and EPb) and UPb in 20 subjects. * and ** indicate significant correlations at levels of p < 0·05 and 0·01, respectively (large sample conservative multiple significance test) Regression lines with 95% confidence limits are additionally shown Conversion to SI units as in table and fig 1.*

(Slide 10)

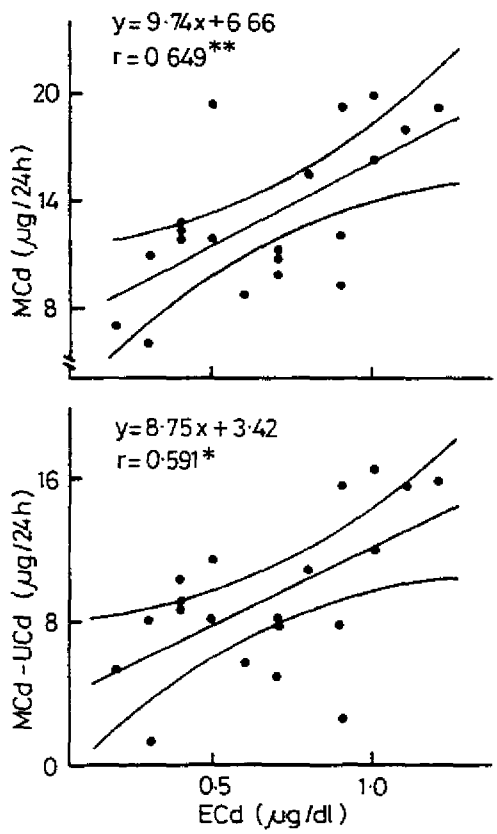


Fig 3 *Correlations of mobilisation yield of cadmium in urine by CaEDTA (MCd) and MCd minus spontaneous urinary excretion of cadmium (UCd) with its erythrocyte concentration (ECd) in 20 subjects. * and ** indicate significant correlations at levels of p < 0·05 and 0 01, respectively (large sample conservative multiple significance test). Regression lines with 95% confidence limits are additionally shown Conversion to SI units as in table and fig 1.*

(Slide 11)

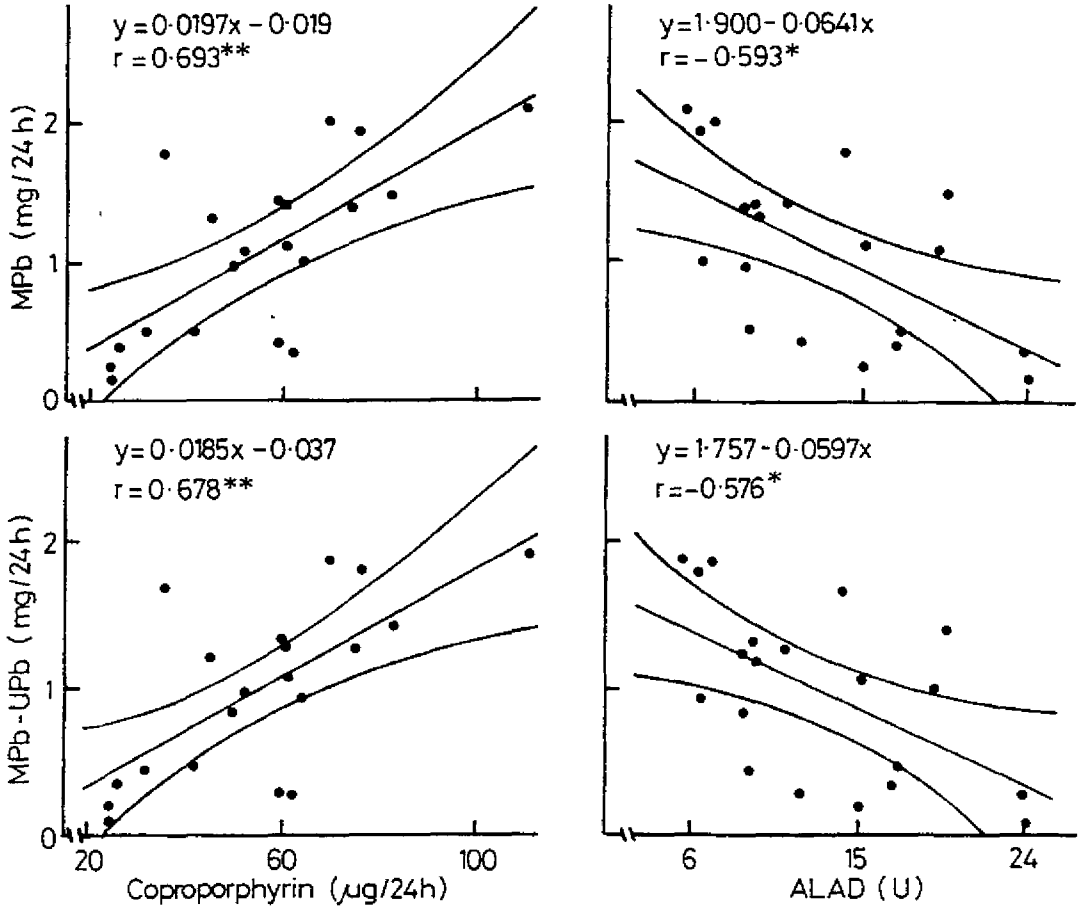


Fig 4 *Correlations of mobilisation yield of lead in urine by CaEDTA (MPb) and MPb minus spontaneous urinary excretion of lead (UPb) with urinary excretion of coproporphyrin and intra-erythrocytic enzyme δ-aminolaevulinic acid dehydratase (ALAD) activity in 20 subjects. * and ** indicate significant correlations at levels of p < 0·05 and 0·01, respectively (large sample conservative multiple significance test) Regression lines with 95% confidence limits are additionally shown. 1 µg/24 h for coproporphyrin corresponds to 1·5 nmol/24 h.*

(Slide 12)

Archives of Environmental Health is published by Heldref Publications, 4000 Albermarle St., N.W., Washington DC 20016.

Behaviour of Lead and Zinc in Plasma, Erythrocytes, and Urine and ALAD in Erythrocytes following Intravenous Infusion of CaEDTA in Lead Workers

SHUNICHI ARAKI, M.D., D.M.Sc., M.Sc.
HIROSHI AONO, M.D., D.M., D.M.Sc.
Department of Public Health and Hygiene
Medical College of Oita
Oita, Japan

MASARU FUKAHORI. M.D.
KOSHIRO TABUKI, B. Agr.
Oita Occupational Health Service
Oita, Japan

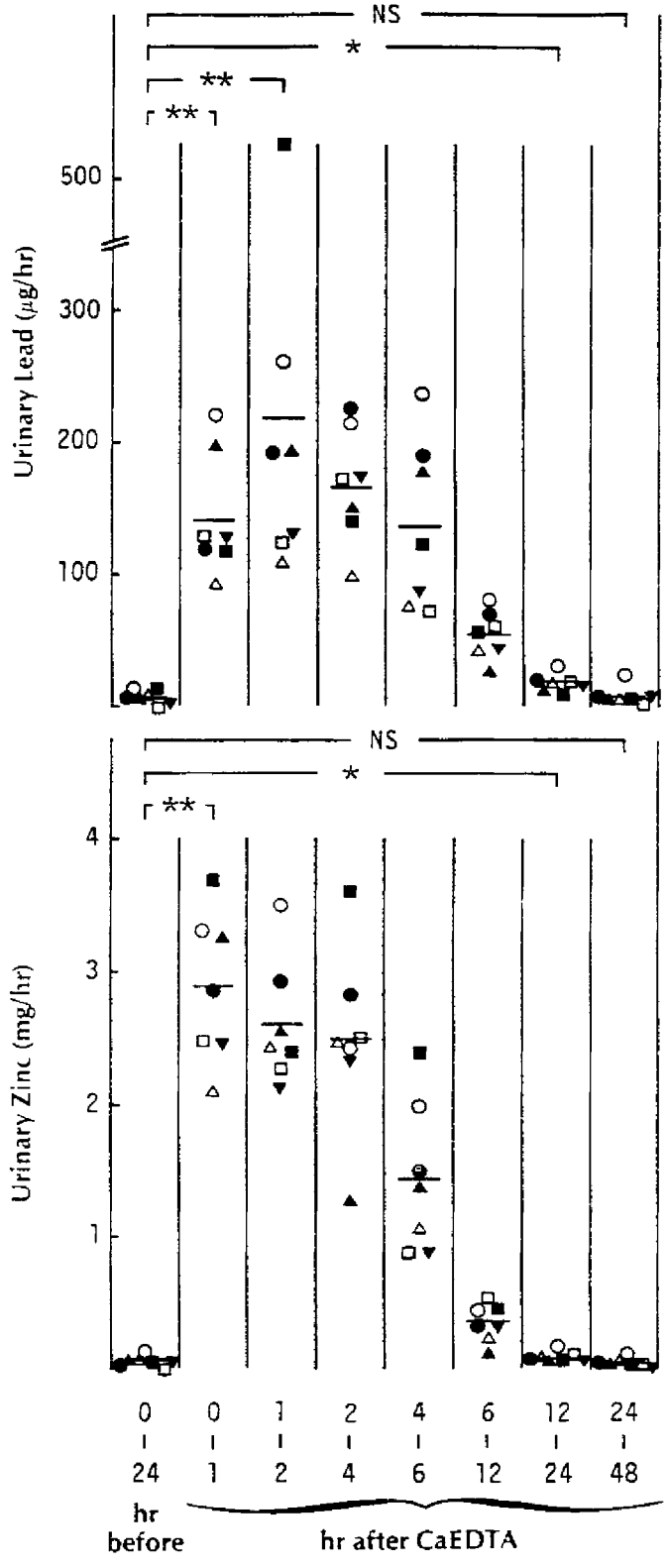


Fig. 1. Urinary excretion of lead and zinc before and after the start of a 1-hr CaEDTA infusion. ○, ●, ∠, ▲, □, ■, and ▼ represent each subject; the *transverse line* in each column indicates a mean value; * and ** are significant differences at the *P* levels < .05 and .02, respectively, by the Wilcoxon signed rank test; NS = no significant difference at a *P* level of .05. The difference in zinc excretion between 0 to 24 hr before and 12 to 24 hr after CaEDTA is statistically significant, even though it is trivial in magnitude.

(Slide 14)

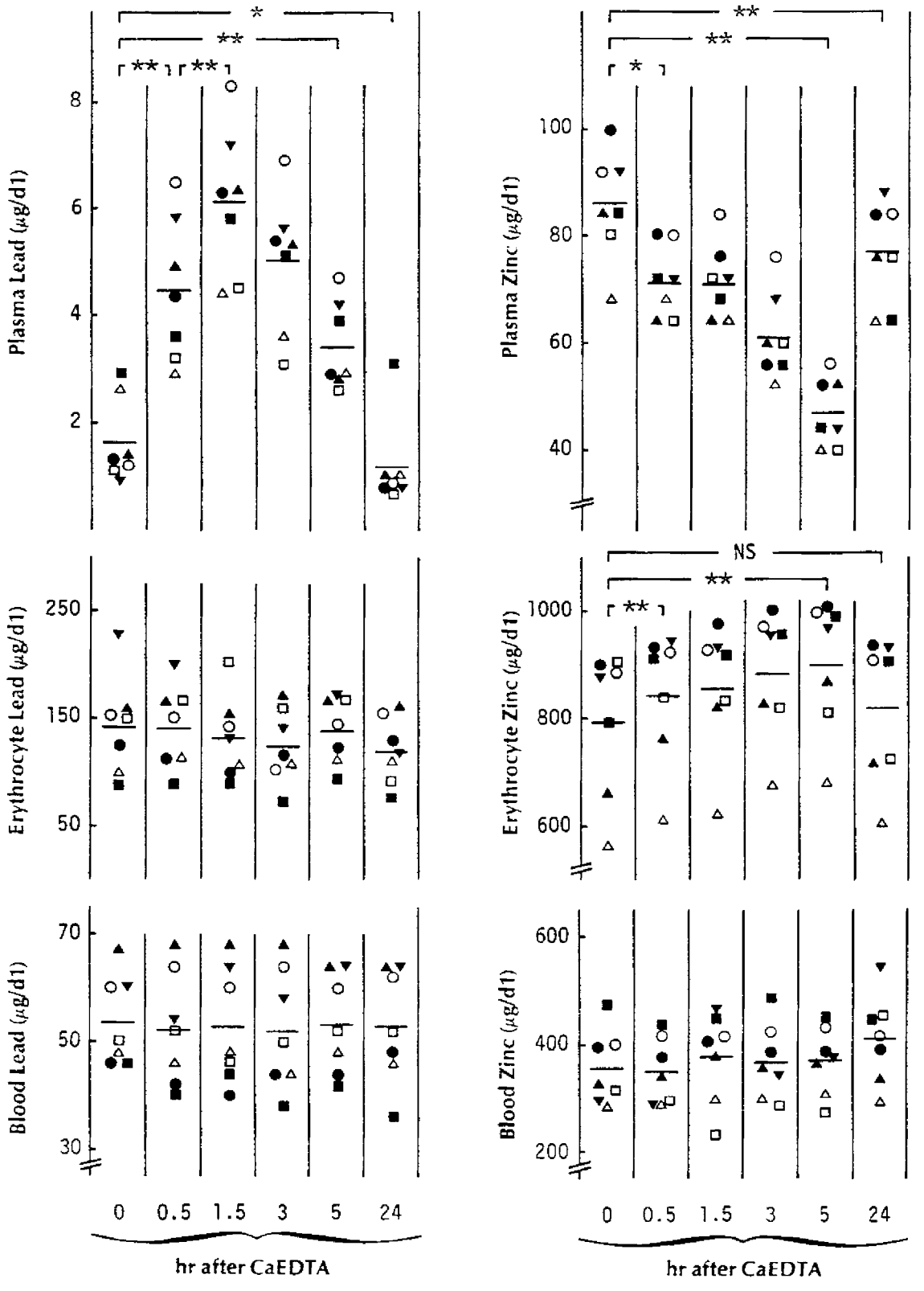


Fig. 2. Alterations in lead and zinc in plasma, erythrocytes, and whole blood after start of 1-hr CaEDTA infusion. (Symbols are defined in legend to Figure 1.)

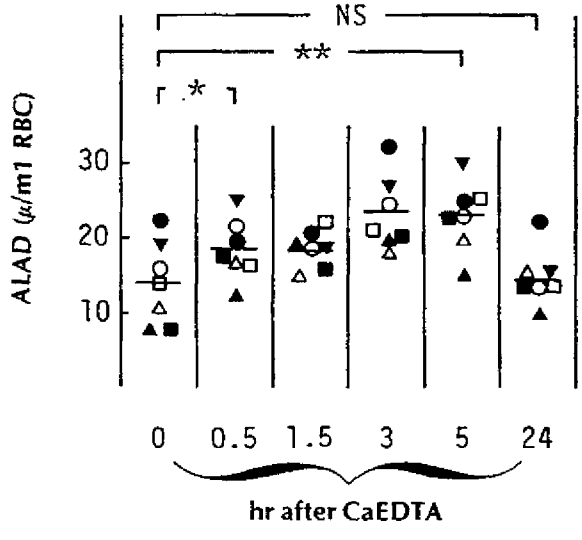


Fig. 3. Alteration in ALAD after start of 1-hr CaEDTA infusion. (Symbols are defined in legend to Figure 1.)

(Slide 16)

British Journal of Industrial Medicine 1982;39:157-160

Assessment of the body burden of chelatable lead: a model and its application to lead workers

S ARAKI[1]* AND K USHIO[2]

From the Department of Public Health,[1] Tohoku University School of Medicine, Seiryo-machi, Sendai 980, and the Tokyo Rosai (occupational diseases and injuries) Hospital,[2] Omori, Ota-ku, Tokyo 143, Japan

(Slide 17)

Table 1 *Estimated values of A and k from study 1: dose of CaEDTA = 53·4 μmol (20 mg) per kg bodyweight*

Subject			*BPb* (*μmol/kg*)	*MPb(1)* (*μmol/24 h*)	*MPb(2)* (*μmol/24 h*)	*A* (*μmol*)	*k*
No	*Age (y)*	*Occupation (y)*					
1	32	Lead smelter (4)	2·9	14·20	12·07	95	0·15
2	64	Lead founder (33)	2·9	16·83	14·43	120	0·14
3	57	Lead smelter (28)	1·5	3·19	2·80	27	0·12
4	59	Welder (26)	0·9	1·63	1·45	15	0·11
5	60	Paint maker (1)	0·8	2·64	2·00	11	0·24
6	68	Type founder (21)	0·5	1·00	0·84	6	0·16
7	43	Stereotype founder (24)	1·7	2·16	1·93	20	0·11
8	44	Enameller (20)	0·3	0·29	0·27	4	0·07
Mean	53		1·4	5·24	4·47	37	0·14

BPb = Blood lead concentration (1 μmol/kg = 21 μg/100 g).
MPb(1) and MPb(2) = Mobilisation yield of lead by CaEDTA on the first day and the second day, respectively (1 μmol/24 h = 207 μg/24 h).
A = Body burden of chelatable lead just before the first CaEDTA injection (1 μmol = 207 μg).
k = Proportion of MPb(1) to A.

(Slide 18)

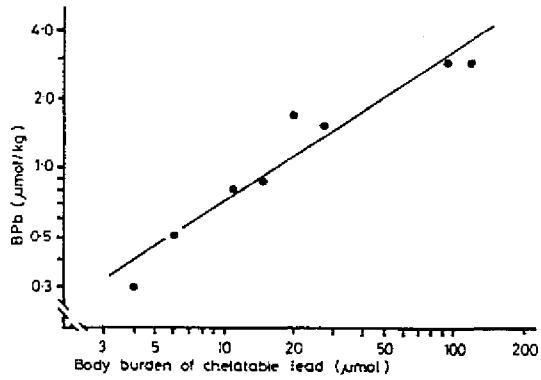


Fig 1 *Relationship between blood lead (BPb) and body burden of chelatable lead (A). Study 1: the regression equation, significance level for the regression coefficient (p) and correlation coefficient (R) are log BPb = 0·650 log A − 0·798 (BPb = 0·159 A $^{0.650}$), p < 0·001 and R = 0·966, respectively.*

(Slide 19)

J. TOXICOL.-CLIN. TOXICOL., 20(5), 475-486 (1983)

A COMPARISON OF THE DIMINUTION RATES OF LEAD IN BLOOD AND LEAD MOBILIZED BY CaEDTA AFTER TERMINATION OF OCCUPATIONAL EXPOSURE: A LONG-TERM OBSERVATION IN TWO LEAD WORKERS

Shunichi Araki, M.D., MSc., Katsuyuki Murata, M.D.,
and Hiroshi Aono, M.D.
Department of Public Health and Hygiene
Medical College of Oita
Hazama-machi, Oita-gun, Oita, 879-56 Japan

Susumu Yanagihara and Koichi Ushio, M.D.
Tokyo Rosai (Occupational Diseases and Injuries) Hospital
Omori, Ota-ku, Tokyo, 143 Japan

(Slide 20)

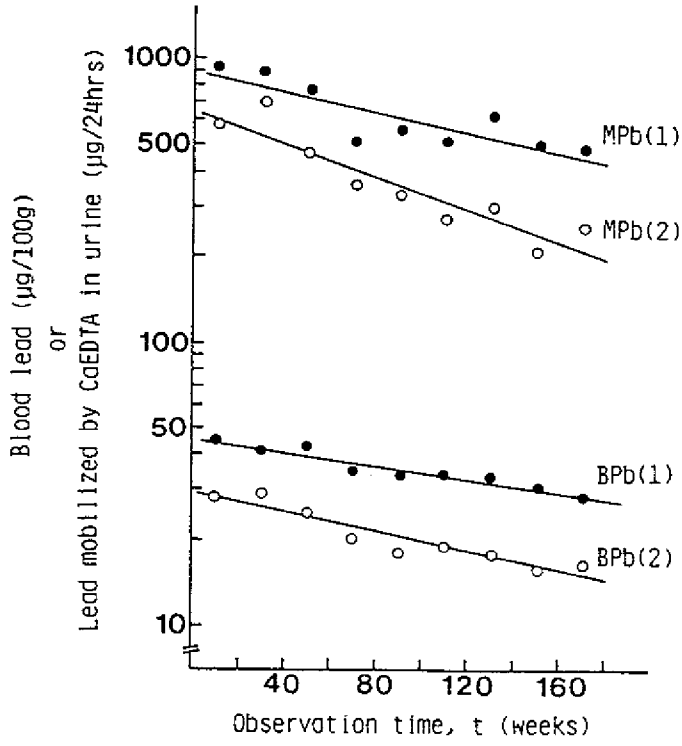


FIGURE 1. Average values of blood lead (BPb) and lead mobilized by CaEDTA in urine (MPb) at each 20-week interval during observation period in Subjects 1 and 2. The numbers 1 and 2 in parentheses show Subjects 1 and 2, respectively. The regression equation, significance level (p) for the regression coefficient and correlation coefficient (R) for each relation are as follows: log BPb (1) = 1.4646 - 0.001749 t, $p < 0.001$, $R = -0.937$; log BPb (2) = 1.6545 - 0.001201 t, $p < 0.001$, $R = -0.961$; log MPb (1) = 2.8143 - 0.002925 t, $p < 0.001$, $R = -0.927$; and log MPb (2) = 2.9510 - 0.001727 t, $p < 0.005$, $R = -0.839$.

(Slide 21)