ORIGINAL

The Effect of Ca- and H₅-DTPA Administered by Various Routes on the Removal of ⁵⁹Fe from the Rat Lung Instilled with ⁵⁹Fe-iron Dextran

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To assess the possibility of application of H₅-DTPA for the chelating treatment in the accidental contamination with radioactive metal elements, the experimental treatments with Ca- and H₅-DTPA were carried out in rats of which lungs were instilled with ⁵⁹Fe-iron dextran. After the instillation, the animals were treated by DTPA on the 2nd day and sacrificed on the 7th day. The lung retention of ⁵⁹Fe was significantly decreased and the urinary excretion was remarkably increased by the intratracheal instillation of Ca-DTPA at doses of 30 and 300 μmol/rat. While the intratracheal instillation of H₅-DTPA of 30, 100 and 150 μmol/rat significantly increased the urinary excretion of ⁵⁹Fe, its effectiveness was about half that of Ca-DTPA. On the other hand, no significant change was observed after either the subcutaneous implantation of H₅-DTPA or intraperitoneal injection of Ca-DTPA at the same dose level.

KEY WORDS: H₅-DTPA, Ca-DTPA, ⁵⁹Fe-iron dextran, intratracheal instillation, rat

I INTRODUCTION

Chelating therapy is one of the most notable treatments for the contamination with heavy metals. Several kinds of chelating agents have been investigated for the purpose of clinical use, *e.g.*, British-Anti-Lewisite (BAL)¹⁾, citric acid,²⁾ ethylenediaminetetraacetic acid (EDTA),^{3,4)} Desferrioxamine B-methane sulfonate (DFOA)^{5,6)} and diethylenetriaminepentaacetic acid (DTPA).^{7,8)} Among these agents, DTPA has many advantages and is suitable for the decontamination of heavy metals, especially of actinide elements. Recently, the zinc trisodium salt of DTPA (Zn-DTPA) has been approved by Food and Drug Administration

of USA for the clinical treatment of actinide contamination in human.⁹⁾ However, it is also well recognized that there is much room for the improvement in the DTPA therapy in order to enhance the removal efficiency and to minimize the side effect.¹⁰⁻¹⁴⁾ In the present study, the experimental chelating therapy was carried out in the rats of which the respiratory tract had been contaminated with intratracheal injection of ⁵⁹Fe-iron dextran colloid. ⁵⁹Fe-iron dextran was used to mimic the polymerized plutonium because not only it is easy to be obtained and safe to be handled, but also it may share a common metabolic pathway with plutonium in reticulo-endothelial phagocytes.¹⁵⁾ Two experiments were undertaken, at first to reconfirm the previous finding that the administration of Ca-DTPA into the respiratory tract is much more effective than the conventional parenteral administration,¹⁰⁾ and secondly to assess the possibility of the use of H₅-DTPA in place of Ca-DTPA.

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It is difficult to sustain the blood concentration of Ca-DTPA in a effective level, since Ca or Zn salt of DTPA is metabolized and excreted into the urine very rapidly.¹⁶⁾ On the other hand, H₅-DTPA, which is a free form of DTPA, is relatively insoluble in water. By the subcutaneous implantation of H₅-DTPA, it could be slowly dissolved in the body fluid and supplied as Ca-DTPA under the coexistence of CaHPO₄. Therefore, it is expected that the administration of H₅-DTPA could sustain the blood concentration of DTPA in the effective level for a longer period than Zn- or Ca-DTPA.

II MATERIALS AND METHODS

1. Preparation of ⁵⁹Fe-iron dextran

Iron-dextran, a ferric hydroxide sol stabilized with dextran, was prepared by the hydrolysis of ferric chloride, according to the procedure described by Priest *et al.*¹⁵⁾ In brief, 2 ml of 1% (w/v) ferric chloride solution containing 7.4 MBq ⁵⁹Fe-ferric chloride (New England Nuclear, U.S.A.) was added to the 20 ml of boiling sodium hydroxide solution (2×10^{-4} M) to give a dark red sol colloid of ferric hydroxide. The sol was dialyzed with distilled water until no free ⁵⁹Fe could be detected in the dialyzate, and stabilized with 2% (w/v) dextran (mol. wt. = 500,000).

2. Instillation of ⁵⁹Fe-iron dextran and DTPA

Male Wistar rats, weighing 310–390 g and supplied from the facility of our institute, were used in this study. The rats were anesthetized with intraperitoneal injection of pentobarbital (25 mg/kg body weight), and 0.5 ml of ⁵⁹Fe-iron dextran colloid suspension (19 kBq, 0.09 mg iron) was instilled into the whole lung via intratracheal cannula.¹⁷⁾ The animals were then isolated individually and given food and water *ad libitum*. Two days after the ⁵⁹Fe-iron dextran instillation, the whole body content of ⁵⁹Fe was measured by counting with whole body counter and defined as the initial body burden (IBB).

Ca-DTPA was dissolved in 0.25 M glucose and 30 to 300 μ mol/0.5 ml/rat was administered by either intraperitoneal injection or the lung instillation as the same manner described above. H₅-DTPA and the same mol of CaHPO₄ was suspended in 0.25 M glucose by the Warling blender and 30 to 150 μ mol/0.5 ml/rat was administered by the lung instillation.

3. Implantation of H₅-DTPA

A half ml of H₅-DTPA suspension containing CaHPO₄ was packed in the cellophane tube (Cellophane Tubing-Seamless, $\phi = 8/32$ inch. Union Carbide Co., U.S.A.). The back of the rat was shaved. Then, approximately 1 cm long incision was made adjacent to the site chosen for the tube placement and a subcutaneous pocket for the tube in desired location was made by inserting a hemostat into one end of the wound. The cellophane tube was inserted into the pocket and the wound was closed with clips.

4. Measurement of ⁵⁹Fe

On the seventh day after the DTPA treatment, the rats were killed by cutting the abdominal aorta under anesthesia. Since DTPA is excreted into the urine rapidly, the effect of DTPA does not continue in the single administration. In the present study, therefore, the effect was judged on the seventh day after the single administration of DTPA. The lungs were lavaged with Dulbecco's calcium and magnesium free phosphate buffered saline (PBS(–)). The lavage fluid was centrifuged to separate the cell pellets from the supernatant. The lung and liver were also dissected free. The feces and urine were separately collected on day 1, 2, 4 and 7 after the DTPA treatment. The radioactivity of ⁵⁹Fe in these samples was measured by scintillation counter (Packard Armac Liquid Scintillation Detector, Model 446, with Tri-Carb Scintillation Spectrometer, Model 3001) and auto γ -well counter (Beckman ND-5500). The distribution, retention and excretion of ⁵⁹Fe were expressed as the percentage of IBB.

III RESULTS

1. The change of distribution of ⁵⁹Fe in the control group

In the control group, the retention of ⁵⁹Fe in the lung and lavage fluid (lavage sup. + bronchio-alveolar cells (BAC)) was about 75 and 12% of IBB on the 9th day after the instillation of ⁵⁹Fe-iron dextran, respectively (Table 1). There was no significant difference in the lung content of ⁵⁹Fe between the 2nd and 9th day after instillation. The total activity of ⁵⁹Fe in the lavage fluid was also at the same level on the 2nd and 9th day after instillation, whereas the ratio of ⁵⁹Fe retention in the supernatant to that in the fraction of BAC was decreased from 2.7 on day 2 to 1.8 on day 9 after instillation. The reten-

Table 1 Change of the retention of ⁵⁹Fe in rats instilled with ⁵⁹Fe-iron dextran.

Day after instillation	No. of rats	Lung	Lavage sup.	BAC	Sup/BAC (ratio)	Liver	Carcass
2nd day	4	75.9±1.1	9.2±1.6	2.8±0.5	4.0±1.3	0.93±0.16	11.3±1.6
9th day	8	75.2±1.3	7.8±0.8	4.7±0.4	1.8±0.3	1.6±0.2	8.4±1.2

Values are mean±s.e.m. and expressed as the percentage of the initial body content of ⁵⁹Fe.

Table 2 Effect of Ca- and H₅-DTPA on the tissue distribution of ⁵⁹Fe in rats following the intratracheal, intraperitoneal injection and subcutaneous implantation (Experiment I).

Treatment	No. of rats	Lung	Lavage sup.	BAC	Sup/BAC (ratio)	Liver	Carcass
Saline	8	75.2±1.3	7.8±0.8	4.7±0.4	1.8±0.3	1.6±0.2	8.4±1.2
Ca-DTPA, I.T. 30 µmol/rat	5	62.8±2.0*	13.7±6.6	4.7±0.7	3.3±0.6	2.8±0.2*	11.5±1.0
300	5	62.8±2.9*	11.6±2.2	3.5±0.6	3.7±1.0*	2.9±0.3*	12.1±1.0
Ca-DTPA, I.P. 30 µmol/rat	2	73.7±0.3	8.5±1.5	7.0±0.3	1.2±0.3	1.6±0.2	7.5±0.4
300	4	75.8±5.1	6.3±1.1	4.0±0.8	1.7±0.3	2.0±0.7	8.3±2.0
H ₅ -DTPA, Implant. 300 µmol/rat	3	80.0±2.5	4.7±0.3	3.2±0.6	1.5±0.3	1.5±0.4	8.4±2.1

Values are mean±s.e.m. expressed as the percentage of the initial body content of ⁵⁹Fe.

*1 denotes significant difference from the control group at $p < 0.005$.

*3 $p < 0.025$.

tion of ⁵⁹Fe in the carcass was decreased from 11.3% of IBB on day 2 to 8.4% on day 9. On the other hand, the retention of ⁵⁹Fe in the liver was increased 0.7% for the seven days, *i.e.* from day 2 to day 9. The urinary and the fecal excretion during the same period was 0.3 and 1.9% of IBB in the control group, respectively.

2. Effect of intratracheal, intraperitoneal injection of Ca-DTPA and implantation of H₅-DTPA (Experiment I)

As shown in **Table 2**, the lung retention of ⁵⁹Fe was not decreased by intraperitoneal injection of Ca-DTPA. The urinary and fecal excretions of ⁵⁹Fe were unchanged. By the implantation of H₅-DTPA, there was also no change in the systemic retention and the excretion of ⁵⁹Fe. On the other hand, **Table 2** shows the intratracheal instillation of Ca-DTPA was significantly effective. The lung retention of ⁵⁹Fe was significantly decreased from 75% of IBB for the control group to approximately 63% for the treated group of 30 or 300 µmol of Ca-DTPA. There was no difference in the effect between these doses. For the distribution in the lavage fluid, the ratio of the retention of ⁵⁹Fe in the supernatant to that in BAC was raised about 2 times that of the control for the both doses. The

liver retention was also increased from 1.6% in control to 2.8% for 30 µmol and 2.9% for 300 µmol.

By the treatment of 300 µmol of Ca-DTPA, the urinary excretion of ⁵⁹Fe was remarkably increased and the excretion on the 1st day after treatment reached 42 times of the control. The results are shown in **Table 3**. For seven days from 2 to 9 day after instillation the total urinary excretion amounted to 3.6% of IBB, whereas it was only 0.31% in the control group for the corresponding period. The total excretion was also increased in the 30 µmol treated group. The ⁵⁹Fe excreted into the feces was significantly increased only in the rats instilled with 300 µmol of Ca-DTPA.

3. Comparison of the effect between Ca-DTPA and H₅-DTPA (Experiment II)

In the second experiment, the animals were instilled with Ca- and H₅-DTPA intratracheally into the lung for comparing the removal effect of both chelating agents. The results are shown in **Tables 4, 5**. There was statistically significant decrease in the lung retention of ⁵⁹Fe in the group treated with 100 and 150 µmol of Ca-DTPA. The decrease of lung retention was greater for Ca-DTPA than for H₅-DTPA. The ratio of

Table 3 Effect of Ca- and H₅-DTPA on the excretion of ⁵⁹Fe in rats following the intratracheal, intraperitoneal injection and subcutaneous implantation (Experiment I).

Treatment	No. of rats	Feces		Urine	
		1st day	Total	1st day	Total
Saline	8	0.52±0.12	1.9±0.2	0.07±0.02	0.31±0.07
Ca-DTPA, I.T. 30 µmol/rat	5	1.8 ±0.8	3.9±1.4	0.87±0.11* ¹	1.4 ±0.1* ¹
300	5	1.4 ±0.4* ⁴	3.5±0.4* ²	2.9 ±0.3* ¹	3.6 ±0.3* ¹
Ca-DTPA, I.P. 30 µmol/rat	2	0.33±0.09	1.4±0.3	0.06±0.02	0.30±0.08
300	4	1.4 ±0.9	3.1±1.3	0.14±0.08	0.49±0.20
H ₅ -DTPA, Implant. 300 µmol/rat	3	0.43±0.18	2.1±0.5	0.06±0.01	0.17±0.02

Values are mean±s.e.m. expressed as the percentage of the initial body content of ⁵⁹Fe.

*¹ denotes significant difference from the control group at $p<0.005$, *² $p<0.01$, *⁴ $p<0.05$.

Table 4 Effect of intratracheal injection of Ca- and H₅-DTPA on the tissue distribution of ⁵⁹Fe in rats (Experiment II).

Treatment	No. of rats	Lung	Lavage sup.	BAC	Sup/BAC (ratio)	Liver	Carcass
Saline	7	87.3±1.7	3.4±0.8	2.0±0.2	1.8±0.4	0.37±0.04	3.8±0.6
Ca-DTPA, I.T. 30 µmol/rat	5	82.9±1.0	5.5±0.9	3.1±0.6	1.9±0.4	0.89±0.15* ¹	5.2±0.9
100	2	76.3±3.9* ³	8.7±1.2	4.1±1.5	2.3±0.6	0.95±0.39* ³	5.0±0.2
150	3	75.4±2.4* ¹	5.8±1.6	1.4±0.7	4.7±1.7* ⁴	1.8 ±0.1* ¹	8.7±0.6* ¹
H ₅ -DTPA, I.T. 30 µmol/rat	5	85.7±0.8	4.5±0.5	3.1±0.4	1.5±0.2	0.53±0.10	3.2±0.4
100	3	84.2±1.5	5.2±0.3	4.7±1.3	1.3±0.3	0.52±0.12	3.2±0.5
150	2	81.9±2.0	3.9±0.1	3.6±0.5	1.1±0.2	0.99±0.28* ¹	5.4±1.3

Values are mean±s.e.m. and expressed as the percentage of the initial body content of ⁵⁹Fe.

*¹ denotes significant difference from the control group at $p<0.005$, *³ $p<0.025$, *⁴ $p<0.05$.

lavage supernatant to BAC was significantly raised only by the treatment with 150 µmol of Ca-DTPA. The total excretion for seven days was also increased significantly by the instillation of 150 µmol of Ca-DTPA and H₅-DTPA (Table 5). In the animals administered with 30 and 100 µmol of Ca-DTPA, the amounts of ⁵⁹Fe excreted to the urine was 18 and 45 times that of the control, respectively, while those were 7.3 and 10 times that of the control in the same doses of H₅-DTPA. The urinary excretion on the 1st day was increased by the treatment of Ca-DTPA instillation from 0.05% of IBB in the control group to 0.55% for 30 µmol, 1.6% for 100 µmol and by 3.4% for 150 µmol. The increments of urinary excretion of ⁵⁹Fe in the H₅-DTPA treated group were smaller than in the Ca-DTPA group, 0.22, 0.30 and 1.1% of IBB for 30, 100 and 150 µmol of H₅-DTPA, respectively. In all the

treated groups the urinary excretion of ⁵⁹Fe for the first 24 h after treatment was also higher than the control one (data are not shown).

IV DISCUSSION

As shown in Tables 1, 3, the amount of ⁵⁹Fe on the 2nd day in the extra-pulmonary tissues, *i.e.*, liver and carcass, is close to the total amount of the ⁵⁹Fe found in these tissues and in the urine and feces on the 9th day. This suggests that the initial clearance had almost finished within the first two days after instillation of ⁵⁹Fe-iron dextran, and only a little amount of ⁵⁹Fe was translocated from the pulmonary region to the other tissues in the successive seven days.

Although the total retention of ⁵⁹Fe in the lung region was unchanged in the control group during the seven days as described above, the ratio of the ⁵⁹Fe content in the supernatant to that in

Table 5 Effect of intratracheal injection of Ca- and H₅-DTPA on the excretion of ⁵⁹Fe in rats (Experiment II).

Treatment	No. of rats	Feces		Urine	
		1st day	Total	1st day	Total
Saline	7	0.32±0.11	2.1±0.3	0.05±0.04	0.07±0.03
Ca-DTPA, I.T. 30 μmol/rat	5	0.29±0.16	1.6±0.2	0.05±0.19* ²	0.72±0.23* ²
100	2	0.52±0.26	2.9±0.9	1.6 ±0.3* ¹	1.8 ±0.3* ¹
150	3	0.71±0.05	3.2±0.4* ⁴	3.4 ±0.5* ¹	3.7 ±0.4* ¹
H ₅ -DTPA, I.T. 30 μmol/rat	5	0.50±0.28	2.6±0.6	0.22±0.07* ⁴	0.29±0.08* ³
100	3	0.26±0.06	1.8±0.1	0.30±0.06* ¹	0.38±0.07* ¹
150	2	0.45±0.14	2.2±0.1	1.1 ±0.1* ¹	1.2 ±0.2* ¹

Values are mean ± s.e.m. expressed as the percentage of the initial body content of ⁵⁹Fe.

*¹denotes significant difference from the control group at $p < 0.005$, *² $p < 0.01$, *³ $p < 0.025$, *⁴ $p < 0.05$.

BAC was decreased from 4.0 on day 2 to 1.8 on day 9. The reason is not readily apparent from the present study, but it may be reasonable to assume the following mechanism. ⁵⁹Fe-iron dextran on the surface of alveolar was ingested by BAC, especially by alveolar macrophages (AM)¹⁸ and stays there for seven days, and even after iron dextran particles were solubilized,¹⁹ the resulting ⁵⁹Fe ions were again retained by the tissue component locally.

The instillation of Ca-DTPA was apparently effective for removing ⁵⁹Fe from the lung region, and for enhancing the excretion from the body. The result shown in **Table 2** suggested the increment of the soluble form of ⁵⁹Fe in the alveolar region after Ca-DTPA instillation. The solubilized ⁵⁹Fe is released from BAC and rapidly bound to DTPA. The resulting Fe-DTPA is translocated from the alveolar space to the vascular circulating system without the redistribution or reuptake into the cells in the pulmonary region.¹⁹ The ⁵⁹Fe-DTPA in the blood is carried away from the lungs, and excreted to the urine or redistributed into the liver where ⁵⁹Fe-DTPA is due to be excreted to the feces.

The Ca-DTPA administered intraperitoneally has little effect on the removal of ⁵⁹Fe from the lung and on the excretion from the body (**Tables 2, 3**). This is because Ca-DTPA cannot reach the alveolar region where almost all of ⁵⁹Fe is located on the 2nd day after the ⁵⁹Fe-iron dextran instillation.

In the Experiment II, the lung retention of ⁵⁹Fe in the control group was 87% of IBB. This

figure is 12% higher than that of control group in the Experiment I. Not only the distribution of ⁵⁹Fe to the lavage, liver and carcass in the control group, but the removal efficiency of Ca-DTPA also differed between the Experiment I and the Experiment II. The reason for this difference is not readily apparent, but a variance in the property of ⁵⁹Fe-iron dextran such as solubility and diameter of colloid particles may be responsible, since the batches of ⁵⁹Fe-iron dextran used in the both experiments were different.

The experimental decorporation therapy using the H₅-DTPA was carried out from the following reason. H₅-DTPA is relatively insoluble and might be phagocytized by AM and released slowly as the chelate form. As a result of slow release from AM, DTPA could be retained in the lung for a longer period and the effect of DTPA may be enhanced. However, as shown in **Tables 4, 5**, the effect of H₅-DTPA on the lung retention and the urinary excretion of ⁵⁹Fe was not higher than that of conventional Ca-DTPA treatment. The lower removal efficiency of H₅-DTPA than Ca-DTPA is possibly attributed, at least in part to the mucociliary clearance of H₅-DTPA. As the H₅-DTPA is insoluble, this agent had to be administered in the particle suspension and the diameter of H₅-DTPA particles in the solution were fairly large. This suggests that a relatively large part of H₅-DTPA could not reach the alveolar region where ⁵⁹Fe exists, and might deposit on the upper respiratory tract and be removed by mucociliary clearance

to the gastro-intestinal tract very rapidly after the instillation.

In this report we have presented the outline dealing with the effect of Ca- and H₅-DTPA on the metabolism of colloidal iron. In practical cases, the repeated administration of DTPA will be required for the removal of incorporated radionuclide. For the purpose of application to the human, therefore, it may be necessary to perform a long-term experiment and to accumulate the data on the effect of repeated administration of DTPA. The dose-effect relationship of the incorporated radionuclide is also an essential research subject from the view point of radiation protection.

V CONCLUSION

It was shown that the lung retention of ⁵⁹Fe was decreased and the urinary excretion was increased by the intratracheal instillation of Ca-DTPA. While the intratracheal instillation of H₅-DTPA increased the urinary excretion of ⁵⁹Fe, its effectiveness was about half that of Ca-DTPA. On the other hand, no significant change was observed after either the subcutaneous implantation of H₅-DTPA or intraperitoneal injection of Ca-DTPA.

REFERENCES

- 1) B. KAWIN and D.H. COPP; Effect of 2,3-dimercaptopropanol (BAL) upon distribution and excretion of plutonium, *Proc. Soc. Exp. Biol. Med.*, **84**, 576 (1953).
- 2) S.S. KETY; The lead citrate complex ion and its role in the physiology and therapy of lead poisoning, *J. Biol. Chem.*, **142**, 181 (1942).
- 3) J.F. HOLLAND, E. DANIELSON and A. SAHAGIAN-EDWARDS; Use of ethylenediaminetetraacetic acid in hypercalcemic patients, *Proc. Soc. Exp. Biol. Med.*, **84**, 359 (1953).
- 4) A. POPOVICI, C.F. GESCHICKTER, A. REINOVSKY and M. RUBIN; Experimental control of serum calcium levels *in vivo*, *Proc. Soc. Exp. Biol. Med.*, **74**, 415 (1950).
- 5) H. KEBERLE; The biochemistry of desferrioxamine and its relation to iron metabolism, *Ann. N. Y. Acad. Sci.*, **119**, 758 (1964).
- 6) M.W. ROSENTHAL and A. LINDENBAUM; Effect of desferrioxamine B-methane sulfonate (DFOM) on removal of plutonium *in vitro* and *in vivo*, *Proc. Soc. Exp. Biol. Med.*, **117**, 749 (1964).
- 7) J.L. FAHEY, C.E. RATH, J.V. PRINCIOITTO, I.B. BRICK and M. RUBIN; Evaluation of trisodium calcium diethylenetriaminepentaacetate in iron storage disease, *J. Lab. Clin. Med.*, **57**, 436 (1961).
- 8) V.H. SMITH; Removal of internally deposited plutonium, *Nature*, **181**, 1792 (1958).
- 9) C.C. LUSHBAUGH and L.C. WASHBURN; FDA IND approval for Zn-DTPA, new clinical agent for decorporation therapy of actinides, *Health Phys.*, **36**, 472 (1979).
- 10) J.W. STATHER, H. SMITH, A.C. JAMES and P. RODWELL; The experimental use of aerosol and liposomal forms of Ca-DTPA as a treatment for plutonium contamination, diagnosis and treatment of incorporated radionuclides, IAEA-SR-6/14, p. 387 (1976).
- 11) S.E. CALDER, G.N. TAYLOR, R.D. LLOYD, R.V. PETERSEN, D.R. ATHERTON and C.W. MAYS; Zn-DTPA administered by slow-release implant, *Health Phys.*, **35**, 785 (1978).
- 12) G.N. STRADLING, J.W. STATHER, S.E. HAM and S.A. SUMNER; The use of Puchel and DTPA for removing ²³⁸PuO₂ from the lungs of hamsters, *Health Phys.*, **41**, 387 (1981).
- 13) R.A. GUILMETTE and B.A. MUGGENBURG; Reduction of Cm translocation from lung by constant infusion of DTPA after inhalation of Cm₂O₃ by rats, *Health Phys.*, **48**, 487 (1985).
- 14) R.A. BULMAN, J.W. STATHER, J.C. STRONG, P. RODWELL, R.J. GRIFFIN and A. HODGSON; Further investigations into the use of Puchel for clearing actinides from lungs, National Radiological Protection Board Annual Research and Development Report 1978, p. 128 (1979).
- 15) N.D. PRIEST and J.W. HAINES; The release of plutonium from macrophages in rats: the effects of changes in iron status, *Health Phys.*, **42**, 415 (1982).
- 16) W. STEVENS, F.W. BRUENGER, D.R. ATHERTON, D.S. BUSTER and G. HOWERTON; The retention and distribution of ²⁴¹Am and ⁶⁵Zn, given as DTPA chelates in rats and of [¹⁴C]DTPA in rats and beagles, *Radiat. Res.*, **75**, 397 (1978).
- 17) S. TAKAHASHI and G. PATRICK; Patterns of lymphatic drainage to individual thoracic and cervical lymph nodes in the rat, *Lab. Animals*, **21**, 31 (1987).
- 18) G.W. RICHTER; The cellular transformation of injected colloidal iron complexed into ferritin and hemosiderin in experimental animals, *J. Exp. Med.*, **109**, 197 (1958).
- 19) H. SATO, Y. KUBOTA, S. TAKAHASHI and O. MATSUOKA; ⁵⁹Fe release from alveolar macrophages ingested ⁵⁹Fe-iron dextran: Enhancement by combination of Ca-DTPA and macrophage activating substances, *J. Radiat. Res.*, **27**, 105 (1986).