Interaction of Chelating Agents with Cadmium in Mice and Rats

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The influence of several chelating agents (CaDTPA, ZnDTPA, CaEDTA, ZnEDTA, DMSA, 4-penicillamine and DMPS, DMP and DDC) on the acute toxicity of CdCl₂ and on the whole body retention and tissue distribution of cadmium after the IV application of ¹¹⁵mCdCl₂ was compared in mice. The chelating agents were applied immediately after the application of cadmium. CaDTPA, ZnDTPA and DMSA appeared to be the most effective antidotes. However, DMSA increased the amount of cadmium retained in kidneys. The treatment of cadmium—poisoned mice with the combination of DMSA (IP) and ZnDTPA (SC) (all the compounds were injected in equimolar dose) decreased the toxicity of cadmium more than treatment with one chelating agent (given in a 2:1 dose). However, by studying the effect of these chelating agents and their combination of the retention and distribution of Cd in mice, it was demonstrated that the combined application of the antidotes showed little or no improvement over the results obtained with the most effective of the individual components. In the urine of rats injected with CdCl₂ and treated with the chelating agents (CaDTPA, ZnDTPA, DMSA), the presence of cadmium complexes was demonstrated. The formation of mixed ligand chelates in vivo was not improved. Experiments in mice given a single injection of ¹¹⁵mCd-labeled Cd complexes of DMPS, DMSA and DTPA showed a high retention of cadmium in the organisms after the IV application of CdDMPS and CdDMSA complexes.

Introduction

In previous papers (1–5) the effect of calcium and zinc complexes of some aminopolycarboxylic acids (APCA) in acute cadmium intoxication and the effect of these compounds on the excretion and distribution of cadmium were compared. The most effective were CaDTPA and ZnDTPA (1,2,5), though CdDTPA was neither the most inert of the cadmium complexes of APCA used nor the least toxic (3). It was also reported that N-acetyl-d,l-penicillamine had no antidotal activity in cadmium intoxication under the conditions used (1,2). The effect of dimercaprol was low (1,2).

The purpose of the present studies was to compare the influence of CaDTPA and ZnDTPA on the toxicity, retention and tissue distribution of cadmium with the effects of some chelating agents containing -SH groups. In the light of recent papers which deal with the use of mixed-ligand chelates (6–9), the effect of the combination of some chelating agents was studied as well. All the compounds were applied in acute experiments in mice and rats. The chelating agents were injected immediately after the cadmium injection. This enabled study of the interaction of this metal with chelating agents in the organism before cadmium is firmly bound in the tissues. Cadmium retention and distribution after the application of some cadmium chelates was also studied.

Materials and Methods

Male mice (SPF, Velaz Prague) (20–22 g) divided into groups of n animals (see tables) were used. In the experiment in which the chromatographic analysis of urine was performed as well as in the experiments in which the effect of chelating agents on cadmium-induced lipid peroxidation was examined, male rats (SPF, Velaz Prague), 130–150 g, were used.
The following chemicals and drugs were used: CdCl₂ • 2.5 H₂O (Lachema, puriss.gr.), D-penicillamine (P) (Koch-Light Lab.), dimercaprol (DMP) (BAL, Boots Pure Drug Co. Ltd.), CaNa₂DTPA and ZnNa₂DTPA (prepared in our laboratory from Chel-DTPA, Geigy), CaNa₂EDTA (Ettalcal, Spofa) and ZnNa₂EDTA (prepared in our laboratory from Chelaton 2, Lachema), dimercaptopropane-sulfonic acid sodium salt (DMPS) (Dimaval, gift from E. Heyl & Co., W. Berlin), meso-2,3-dimercaptosuccinic acid (DMSA) prepared by us as sodium salt by dissolving in saline with equivalent amount of NaHCO₃ (gift from Fluka AG, Buchs, Switzerland), diethyldithiocarbamate sodium salt (Lachema, puriss.gr.).

In the cadmium excretion and distribution study ¹¹⁵mCdCl₂ (with carrier) (The Radiochemical Centre, Amersham, England) was used. The radioactivity in the whole body and in various organs after the IV application of 0.5 mg Cd²⁺/kg (approximately 37 kBq per mouse) was measured by using a scintillation spectrometer with NaI (TI) detector (10). The ¹¹⁵mCd-labeled complexes of DMPS and DMSA were prepared by the addition of equivalent amounts of these compounds to the ¹¹⁵mCdCl₂ saline solution. The results are expressed in percent of applied dose.

The same method as described previously (5,11) was used for the chromatographic analysis of urine.

The estimation of malondialdehyde as a product of lipoperoxidation was performed in homogenized liver of rats after 2 hr of incubation at pH 7.4 (12,13).

The effect of some chelating agents on the renal tissue of cadmium-treated mice was determined. Histopathological study after staining with hematoxylin and eosin and after a special histochemical staining to determine the activity of various intracellular enzymes was performed.

Survival of mice was recorded at the end of 10 days. All results were statistically evaluated (Student's t-test, χ² test, Fisher's test). The values given are means ± 95% limits.

## Results

### Influence of Chelating Agents on Acute Toxicity of CdCl₂ in Mice

The effect of P, DMP, CaEDTA, ZnEDTA, CaDTPA and ZnDTPA on the cadmium toxicity was compared (Table 1). In this experiment CaDTPA and ZnDTPA appeared to be the most effective antidotes. No protective effect was observed after the administration of ZnEDTA and P.

In the next experiment, the influence of CaDTPA, ZnDTPA, DMPS and DMSA injected in doses corresponding to the various chelator:Cd molar ratios was investigated (Table 2). CaDTPA was the most effective agent of the chelators studied when low doses (1:1, 1:2) were used. No protective effect was observed with administration of DMPS at these lower doses. High protection was seen with DMSA at a dose corresponding to a molar ratio of 5:1. After the application of this higher dose the order of efficacy of chelators was found to be:

DMSA > CaDTPA > ZnDTPA > DMPS.

The results of experiments in which the protective effect of DDC, CaDTPA and ZnDTPA in cadmium intoxication was compared is shown in Table 3. DDC applied simultaneously or 2 hr after the administration of cadmium was ineffective. DTPA complexes provided protection only after the simultaneous application with Cd.

### Table 1. Effect of chelating agents on survival of mice injected with CdCl₂

| Group and treatment | 10 day survival ratio | % survival | Significance (group:group) |
|---------------------|-----------------------|------------|---------------------------|
| 1 Cd only           | 1/20                  | 5          | NS†                      |
| 2 Cd + D-penicillamine | 3/20                | 15         | 3:1*                     |
| 3 Cd + dimercaprol  | 6/20                  | 30         | 4:1†                     |
| 4 Cd + CaEDTA       | 10/20                 | 50         | 4:6†                     |
| 5 Cd + ZnEDTA       | 5/20                  | 25         | NS                       |
| 6 Cd + CaDTPA       | 17/20                 | 85         | 6:1†                     |
| 7 Cd + ZnDTPA       | 15/20                 | 75         | 6:4†                     |

*Chelating agents were applied IP immediately following SC injection with CdCl₂ • 2.5 H₂O (20 mg/kg) at a chelator:Cd molar ratio of 25:1.

*P < 0.05.

†P < 0.01.

‡NS = p > 0.05.
Table 2. Effect of chelating agents given in various doses on survival of mice injected with CdCl₂.

| Experiment | Group and treatment | Molar ratio chelator:Cd | 10 day survival ratio | % survival | Significance (group:group) |
|------------|---------------------|-------------------------|-----------------------|------------|---------------------------|
|            | 1 Cd only           | —                       | 0/20                  | 0          | —                         |
|            | 2 Cd + CaDTPA       | 1:1                     | 20/33                 | 60.6       | 2:1†                      |
|            | 3 Cd + ZnDTPA       | 1:1                     | 2/33                  | 6.06       | NS†                       |
|            | 4 Cd + DMSA         | 1:1                     | 1/33                  | 3.03       | NS†                       |
|            | 5 Cd + DMPS         | 1:1                     | 0/33                  | 0          | NS†                       |
|            |                     |                         |                       |            |                           |
|            | 6 Cd only           | —                       | 0/20                  | 0          | —                         |
|            | 7 Cd + CaDTPA       | 2:1                     | 16/20                 | 80         | 7:6†                      |
|            | 8 Cd + ZnDTPA       | 2:1                     | 4/20                  | 20         | 8:6*                      |
|            | 9 Cd + DMSA         | 2:1                     | 7/20                  | 35         | 9:6†                      |
|            | 10 Cd + DMPS        | 2:1                     | 0/15                  | 0          | NS†                       |
|            |                     |                         |                       |            |                           |
|            | 11 Cd only          | —                       | —                     | 0          | —                         |
|            | 12 Cd + CaDTPA      | 5:1                     | 27/33                 | 81.82      | 12:11†                    |
|            | 13 Cd + ZnDTPA      | 5:1                     | 20/33                 | 60.67      | 13:11†                    |
|            | 14 Cd + DMSA        | 5:1                     | 33/33                 | 100.0      | 14:11†                    |
|            | 15 Cd + DMPS        | 5:1                     | 4/20                  | 20.0       | 15:11†                    |

*aChelating agents were applied IP immediately following SC injection with CdCl₂·2.5 H₂O (20 mg/kg) at various chelator:Cd molar ratios.

*p < 0.05.
†p < 0.01.
NS = p > 0.05.

Table 3. Effect of the combination of chelating agents on survival of mice which received CdCl₂.

| Experiment | Group and treatment | Molar ratio chelator:Cd | 10 day survival ratio | % survival | Significance (group:group) |
|------------|---------------------|-------------------------|-----------------------|------------|---------------------------|
|            | 1 Cd only           | —                       | 0/20                  | 0          | —                         |
|            | 2 Cd + ZnDTPA       | 2:1                     | 12/20                 | 60         | 2:1†                      |
|            | 3 Cd + DMSA         | 2:1                     | 13/20                 | 65         | 3:1†                      |
|            | 4 Cd + ZnDTPA + DMSA| 1:1:1                   | 19/20                 | 95         | 4:2*                      |
|            |                     |                         |                       |            | 4:3*                      |
|            | 5 Cd only           | —                       | 0/20                  | 0          | —                         |
|            | 6 Cd + CaDTPA       | 1:1                     | 12/20                 | 60         | 6:5†                      |
|            | 7 Cd + DMSA         | 1:1                     | 6/20                  | 30         | 7:5*                      |
|            | 8 Cd + CaDTPA + DMSA| 0.5:0.5:1              | 10/20                 | 50         | 8:6†                      |
|            |                     |                         |                       |            |                           |
|            | 9 Cd only           | —                       | 0/20                  | 0          | —                         |
|            | 10 Cd + ZnDTPA      | 2:1                     | 4/20                  | 20         | 10:9*                     |
|            | 11 Cd + DMPS        | 2:1                     | 0/20                  | 100        | NS†                       |
|            | 12 Cd + DMPS + ZnDTPA| 1:1:1                  | 0/20                  | 100        | NS†                       |

*aChelating agents were applied IP immediately following SC injection with CdCl₂·2.5 H₂O (20 mg/kg) at various chelator:Cd molar ratios.

*p < 0.05.
†p < 0.01.
NS = p > 0.05.
Table 4. Effect of simultaneous and subsequent administration of sodium diethylthiocarbamate (DDC), CaDTPA and ZnDTPA on survival of mice receiving CdCl₂.

| Group            | 10 day survival ratio | % survival | Significance (group/group) |
|------------------|-----------------------|------------|----------------------------|
| Experiment A:<br>1. Cd only | 0/15| 0 | — |
| 2. DDC | 1/15| 6.7 | NS |
| 3. CaDTPA | 13/15| 86.7 | 3:1† |
| 4. ZnDTPA | 12/15| 80.0 | 4:1† |

Experiment B:<br>1. Cd only | 0+/15| 0 | — |
| 2. DDC | 0+/15| 0 | NS |
| 3. CaDTPA | 3+/15| 20 | NS |
| 4. ZnDTPA | 3+/15| 20 | NS |

*Chelating agents were applied IP at chelator:Cd molar ratio of 5:1 after SC administration of CdCl₂ · 2.5H₂O (20 mg/kg).<br>†p < 0.01.<br>aChelating agents applied immediately following cadmium injection.<br>bChelating agents applied 2 hr after cadmium injection.

Table 4 shows the results of the experiment in which the combination of ZnDTPA and DTPA was administered. The additive effect of these two chelating agents was demonstrated. This was shown neither after the application of ZnDTPA + DMPS nor after the injection of CaDTPA + DMSA.

**Influence of Chelating Agents and Their Combinations on Retention and Tissue Distribution of Cd in Mice**

The effect of the chelating agents (P, DMPS, CaDTPA) on the whole body retention and on the content of cadmium in various organs 48 hr after the administration of CdCl₂ is shown in Table 5. No effect of P on the cadmium retention was seen. P as well as DMPS enhanced the amount of cadmium retained in kidneys. CaDTPA was found to be the most effective agent of the chelators used in this experiment.

The results obtained in a similar experiment are summarized in Table 6. The influence of DMPS, DMSA, CaDTPA and ZnDTPA on the re-

| Group and treatment | Total body burden of cadmium, %<br>48 hr after the application of CdCl₂ | Cd content of tissues, %<br>Liver | Gastrointestinal tract | Kidneys |
|---------------------|--------------------------------|-----------------|-----------------|-----------|
| 1 Cd only           | 78.50 ± 5.20                  | 44.24 ± 3.20    | 7.10 ± 2.00     | 2.67 ± 0.70 |
| 2 Cd + D-penicillamine | 80.70 ± 3.10                 | 41.52 ± 2.63    | 6.20 ± 1.32     | 6.55 ± 1.70* |
| 3 Cd + dimercaprol  | 48.30 ± 4.30                  | 25.18 ± 1.91    | 1.94 ± 0.40     | 6.74 ± 0.93* |
| 4 Cd + CaDTPA       | 12.70 ± 1.43                  | 7.74 ± 0.54     | 0.89 ± 0.28     | 0.64 ± 0.10* |

*Chelating agents were applied IP immediately following IV injection of ¹¹⁵mCdCl₂ · 2.5 H₂O (0.5 mg Cd/kg) at a chelator:Cd molar ratio of 50:1; n = 7 for each group.<br>bExpressed as % of dose applied; values represent the mean ± 95% confidence limits.<br>aSignificantly different from the control at p < 0.05.

Table 6. Effect of chelating agents and their combination on total body burden and tissue content of cadmium in mice 24 hr after the application of CdCl₂.

| Group and treatment | Total body burden of Cd, %<br>24 hr after the application of CdCl₂ | Cd content of tissues, %<br>Liver | Gastrointestinal tract | Kidneys |
|---------------------|--------------------------------|-----------------|-----------------|-----------|
| 1 Cd only           | 89.57 ± 6.10                  | 52.22 ± 5.63    | 10.25 ± 1.13    | 6.35 ± 0.91 |
| 2 Cd + DMPS IP      | 83.28 ± 7.80                  | 41.67 ± 4.61*   | 7.34 ± 0.80*    | 8.83 ± 1.12 |
| 3 Cd + CaDTPA SC    | 33.38 ± 9.15*                | 17.33 ± 5.36*   | 3.41 ± 1.08*    | 3.87 ± 1.18* |
| 4 Cd + CaDTPA SC + DMPS IP | 24.50 ± 4.40* | 13.52 ± 3.48* | 2.40 ± 0.74*    | 2.75 ± 0.54* |
| 5 Cd + DMSA IP      | 64.51 ± 7.21*                | 28.23 ± 4.64*   | 6.16 ± 1.07*    | 9.73 ± 1.32 |
| 6 Cd + CaDTPA SC + DMSA IP | 22.01 ± 2.10* | 9.52 ± 1.53* | 2.30 ± 0.27*    | 3.21 ± 0.42* |
| 7 Cd + ZnDTPA       | 44.73 ± 2.84*                | 24.82 ± 1.79*   | 5.12 ± 0.70*    | 4.05 ± 1.04* |

*Chelating agents were applied IP immediately following the IV injection of ¹¹⁵mCdCl₂ · 2.5 H₂O (0.5 mg Cd/kg) at a chelator:Cd molar ratio of 10:1; n = 8 for all groups.<br>bExpressed as % of dose applied; values represent the mean ± 95 confidence limits.<br>aSignificantly different from the control at p < 0.05.
tention and distribution of cadmium was determined. The most effective appeared to be CaDTPA and the DMSA + CaDTPA combination. No increase in excretion of cadmium was seen after DMPS. However, treatment with this chelating agents significantly reduced the amount of cadmium found in the liver and gastrointestinal tract and increased the amount of cadmium in kidneys and in other organs. Similarly, all the compounds used decreased the amount of cadmium in the liver and in the gastrointestinal tract. DMSA increased the amount of cadmium retained in the kidneys. The agents which decreased the content of cadmium in the kidneys were CaDTPA, ZnDTPA and the combinations CaDTPA + DMPS and CaDTPA + DMSA.

The results obtained in the experiment in which the effect of the combination of ZnDTPA and DMSA was examined are shown in Table 7. The influence of this combination on the cadmium retention was compared with the effects of single agents given alone.

ZnDTPA applied at a dose of 5:1 was not effective. The effect of the combination ZnDTPA + DMSA was not better than that of ZnDTPA. DMSA increased the content of cadmium in the kidneys in all cases. The effect of CaDTPA (5:1) was the same as that of ZnDTPA (10:1). The amount of cadmium retained in the liver was decreased after the application of the compounds.

Another experiment demonstrated (Table 8) that the combination of ZnDTPA + DMSA (5:5:1) is more effective than DMSA (10:1). However, the effect of that combination did not reach the effect of ZnDTPA (10:1). After the application of DMSA (either alone or in combination) the content of cadmium in the kidneys was elevated.

### Chromatographic Analysis of Rat Urine after Administration of CdCl₂ and Chelating Agents

In the urine of rats given CdCl₂ + 2.5 H₂O (10 mg/kg; SC) and treated with CaDTPA, ZnDTPA, DMSA (5:1) or with the combination of CaDTPA + DMSA and ZnDTPA + DMSA (5:5:1) the Cd complexes of DMSA and DTPA were detected by paper chromatography. The properties of CdDMSA complexes are different from those of CdDTPA. An extremely slow flow rate of

### Table 7. Effect of chelating agents and their combination on total body burden and tissue content of cadmium in mice 24 hr after the application of CdCl₂.a

| Group          | Molar ratio chelator: Cd | Total body burden of Cd, %b | Liver | Gastrointestinal tract | Kidneys |
|----------------|--------------------------|------------------------------|-------|------------------------|---------|
| 1 Cd only      | —                        | 88.12 ± 4.85                | 42.91 ± 5.27 | 11.15 ± 1.38 | 4.86 ± 1.49 |
| 2 Cd + DMSA SC | 5:1                      | 71.38 ± 8.34*               | 35.81 ± 6.10* | 6.99 ± 1.51* | 10.36 ± 3.47* |
| 3 Cd + ZnDTPA IP | 5:1                    | 57.79 ± 7.13*               | 31.84 ± 7.27* | 7.12 ± 1.73* | 5.59 ± 0.97 |
| 4 Cd + ZnDTPA IP + DMSA SC | 5:5:1            | 59.53 ± 6.77*               | 29.32 ± 4.54* | 6.26 ± 1.37* | 7.96 ± 2.24* |
| 5 Cd + ZnDTPA IP + DMSA SC | 10:1         | 33.49 ± 4.54*               | 16.50 ± 5.43* | 3.91 ± 1.61* | 3.01 ± 0.54* |
| 6 Cd + CaDTPA IP | 5:1                      | 37.63 ± 9.77*               | 22.94 ± 6.93* | 3.94 ± 1.13* | 2.09 ± 1.09* |

*aChelating agents were applied immediately following the IV injection of 110mCdCl₂ · 2.5 H₂O (0.5 mg Cd/kg) at various chelator: Cd molar ratios; n = 7 for all groups.

*bExpressed as % of dose applied; values represent the mean ± 95% confidence limits.

*Significantly different from the control at p < 0.05.

### Table 8. Effect of chelating agents and their combination on total body burden and tissue content of cadmium in mice 24 hr after the application of CdCl₂.a

| Group          | Molar ratio chelator: Cd | Total body burden of Cd, %b | Liver | Gastrointestinal tract | Kidneys |
|----------------|--------------------------|------------------------------|-------|------------------------|---------|
| 1 Cd only      | —                        | 88.12 ± 4.85                | 42.91 ± 5.27 | 11.15 ± 1.38 | 4.86 ± 1.49 |
| 2 Cd + ZnDTPA IP | 10:1                    | 33.45 ± 2.36*               | 16.50 ± 5.50* | 3.91 ± 2.30* | 3.01 ± 0.54* |
| 3 Cd + DMSA SC | 10:1                      | 60.81 ± 2.73*               | 23.11 ± 3.81* | 4.80 ± 0.70* | 10.53 ± 1.99 |
| 4 Cd + ZnDTPA IP + DMSA SC | 5:5:1            | 50.36 ± 4.66*               | 17.84 ± 5.10* | 5.62 ± 0.50* | 8.04 ± 0.66* |

*aChelating agents were applied immediately following the IV injection of 110mCdCl₂ · 2.5 H₂O (0.5 mg/kg) at various chelator: Cd molar ratios; n = 8 for all groups.

*bExpressed as % of dose applied; values represent the mean ± 95% confidence limits.

*Significantly different from the control at p < 0.05.
Table 9. Effect of chelating agents on cadmium-induced lipid peroxidation in kidneys of rats 48 hr after application.*

|                     | Control | Cd | Cd + CaDTPA | Cd + ZnDTPA | Cd + DMSA |
|---------------------|---------|----|-------------|-------------|-----------|
| µg malondialdehyde/g tissue |          |    |             |             |           |
| Retention           | 38.7 ± 5.7  | 89.8 ± 9.8* | 33.6 ± 4.8 | 31.4 ± 9.8 | 46.0 ± 13.3 |
| %b                  | n = 8    | n = 5 | n = 8       | n = 8       | n = 8     |

*aChelating agents were applied IP immediately following the SC injection of CdCl₂·2.5 H₂O (7.5 mg/kg) at a chelator: Cd molar ratio of 5:1.

The independent formation of CdDTPA, DMSA, and CaDTPA were effective in preventing cadmium-induced lipid peroxidation (Table 9).

**Histopathological Examination of Mouse Renal Tissue**

In a preliminary experiment, mice were injected with CdCl₂·2.5 H₂O at a dose of 5 mg/kg SC alone or in the combination with the chelating agents CaDTPA, ZnDTPA, or DMSA (5:1 IP). The kidneys were removed 48 hr after the treatment. No histopathological changes were found in any case when the hematoxylin and eosin staining was used. A slight reduction of the activity of acid phosphatase in the renal tubules was demonstrated after the application of cadmium and CaDTPA. No changes in the activity of glutamate dehydrogenase, α-glycerol phosphate dehydrogenase and nicotinamide adenine dinucleotide reductase were found.

**Retention and Tissue Distribution of Cd after Administration of Cd Chelates**

In this experiment, ¹¹⁵mCdCl₂ and ¹¹⁵mCd-labeled cadmium chelates were administered IV to mice. The results are shown in Table 10. The highest cadmium excretion was found after the injection of CaDTPA. The total body burden of cadmium after the administration of Cd (DMPS)₁ and CdDMSA complexes did not differ significantly from that estimated after the administration of CdCl₂. The whole body retention of cadmium after the administration of Cd (DMPS)₃ was lower than that of the controls. The amount of cadmium retained in the kidneys was elevated after the injection of Cd (DMPS)₃, Cd(DMSA)₁ and Cd(DMPS)₃.

**Discussion and Conclusions**

The results confirm our earlier findings with regard to the efficiency of CaDTPA and ZnDTPA in acute cadmium intoxication (5). DMSA was more effective than CaDTPA when applied in
higher doses. However, the content of cadmium in the kidneys was elevated after the application of this agent. Our results are in agreement with the finding of other authors (8,9,14,15). However, we were not able to demonstrate a positive effect of DMSA on the cadmium content in the kidneys (14). All the chelating agents containing sulphydryl groups increase the cadmium content in the kidneys.

We were unable to confirm the increase in the effectiveness of DDC as an antidote when treatment is delayed after administration of cadmium (16,17). The effectiveness of the DTPA complexes decreases with increasing interval between the injection of cadmium and these agents. This result is in agreement with our earlier findings (4).

The mobilizing and protective effect of ZnDTPA in cadmium intoxication is based predominantly on the kinetic lability of this complex which facilitates the exchange of the metal bound in chelate (pseudoisotopic exchange) (5).

Neither the formation of mixed ligand chelates in vivo nor the potentiation of the effectiveness after the simultaneous application of two chelators was shown. Only the combination of ZnDTPA + DMSA in acute cadmium intoxication improved the effect achieved with one chelator alone.

There is considerable speculation and controversy regarding the mode of toxic action of heavy metals. One mechanism suggested is that toxicity of some heavy metals may be mediated through peroxidation of membrane lipids. We have demonstrated the cadmium-induced lipid peroxidation in liver of rats. This effect of cadmium was vitiated by the pretreatment with zinc chloride (13). The protective effect of chelating agents on the cadmium-induced lipid peroxidation in kidneys was demonstrated.

Even though the amount of cadmium in kidneys is enhanced due to DMSA in mice, the cadmium-induced lipid peroxidation in kidney tissue was decreased after the administration of cadmium and DMSA in rats. The properties of the CdDMSA complex formed in course of the detoxication of cadmium merit further examination.

The protective effect of DMSA in cadmium-induced lipid peroxidation is probably caused by the binding of cadmium. However, a direct effect of DMSA on the lipid peroxidation is not excluded.

The results of our experiments form a basis for the selection of agents which might be used in further studies of the mobilization of cadmium from old deposits in the organism.

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