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The comparative toxicology of ethyl- and methylmercury

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Abstract. Neurotoxicity and renotoxicity were compared in rats given by gastric gavage five daily doses of 8.0 mg Hg/kg methyl- or ethylmercuric chloride or 9.6 mg Hg/kg ethylmercuric chloride. Three or 10 days after the last treatment day rats treated with either 8.0 or 9.6 mg Hg/kg ethylmercury had higher total or organic mercury concentrations in blood and lower concentrations in kidneys and brain than methylmercury-treated rats. In each of these tissues the inorganic mercury concentration was higher after ethyl- than after methylmercury.

Weight loss relative to the expected body weight and renal damage was higher in ethylmercury-treated rats than in rats given equimolar doses of methylmercury. These effects became more severe when the dose of ethylmercury was increased by 20%. Thus in renotoxicity the renal concentration of inorganic mercury seems to be more important than the concentration of organic or total mercury. In methylmercury-treated rats damage and inorganic mercury deposits were restricted to the P_2 region of the proximal tubules, while in ethylmercury-treated rats the distribution of mercury and damage was more widespread.

There was little difference in the neurotoxicities of methylmercury and ethylmercury when effects on the dorsal root ganglia or coordination disorders were compared. Based on both criteria, an equimolar dose of ethylmercury was less neurotoxic than methylmercury, but a 20% increase in the dose of ethylmercury was enough to raise the sum of coordination disorder scores slightly and ganglion damage significantly above those in methylmercury-treated rats.

In spite of the higher inorganic mercury concentration in the brain of ethylmercury- than in the brain of methylmercury-treated rats, the granular layer damage in the cerebellum was widespread only in the methylmercury-treated rats. Thus inorganic mercury or dealkylation cannot be responsible for granular layer damage in alkylmercury intoxication. Moreover, histochemistry demonstrated no inorganic mercury deposits in the granular layer.

Key words: Methylmercury – Ethylmercury – Neurotoxicity – Renotoxicity – Decomposition

Introduction

The neurological signs and symptoms of methyl- and ethylmercury intoxication are identical, but epidemiological-clinical studies from Iraq (Jalili and Abbasi 1961; Damluji 1962; Bakir et al. 1973) indicate that renal function is affected only by ethylmercury. The reason for this may be the faster renal accumulation and/or decomposition of ethylmercury. Thus it has been shown by Suzuki et al. (1963) that the kidneys of mice accumulated more mercury after the administration of ethylmercury than after methylmercury and by Fang and Fallin (1974) that in tissue slices incubated with these alkylmercurials the decomposition of ethylmercury was more noticeable. If this difference in decomposition is present in vivo, the comparative study of their metabolism and toxicity may be a valuable approach to investigate the role of decomposition not only in renal but also in neurotoxicity. It has been proposed by Jacobs et al. (1975) that the lipophilic methylated mercury allows the delivery of mercury to the central nervous system, where damage is caused by the cleaved Hg^{2+}, and by Ganther (1978) that cleavage through free radical formation is responsible for the neurotoxicity of methylmercury.

The purpose of the present study was to compare total and inorganic mercury concentrations in selected tissues, including the brain, after the daily administration of methylmercury or ethylmercury and to relate these findings to damage in brain and kidney.

It was planned that the effects of five daily doses of ethylmercury would be compared at two dose levels with those of 8.0 mg Hg/kg methylmercury, namely when the ethylmercury dose is equimolar with the dose of methylmercury and when the dose gives approximately the same total mercury concentration in brain as found in rats treated with 8.0 mg Hg/kg methylmercury. However, in preliminary experiments it was found that rats can tolerate 9.6 mg Hg/kg ethylmercury, while a further increase in dose to 11.2 mg Hg/kg caused high mortality within 3 days.

Material and methods

Porton Wistar male and female rats were given by gastric gavage five daily doses of 8.0 mg Hg/kg as methylmercuric chloride or 8.0 or 9.6 mg Hg/kg as ethylmercuric chloride (Pierce and Warriner Ltd.) in a volume of 2.0 ml/kg glycerol formol (Fluka A. G.). Animals were kept on MRC 41B diet during the whole experimental period with food and water freely available. The range of initial body weights was 181–231 g for males and 180–220 g for females with 210 g and 196 g means, respectively.

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A. Body weight. Body weights of 24 male and 18 female rats per treatment group were measured five times per week from the 1st treatment day. Because of respiratory problems (wheezing) three male rats had to be sacrificed before schedule and were omitted from comparison. As daily weight gains depend on initial body weight and sex, body weights on 0, 5 and 10 days after the last treatment were related to the normal weight curves supplied by our animal house. A substantial decrease in the standard error of means justified this approach.

B. Coordination disorders. Flailing reflex and hind leg crossing were scored from the last treatment day as described previously (Magos et al. 1978).

C. Histology and histochemistry. All animals were killed by decapitation, with the exception of those perfused for the histological examination of brain and dorsal root ganglia. After decapitation blood was collected in a weighed beaker and stored together with brain and kidneys at −4 °C until assay. Kidneys for histology and kidneys and brain for the histochemical demonstration of mercury were fixed in buffered formalin for 14 days. Slices between 3 and 5 mm thickness were processed and embedded in paraffin wax blocks. From these blocks 5 μm thick sections were cut and either stained with haemotoxylin and eosin or developed for the demonstration of mercury by the method of Danscher and Schroder (1979) with slight modifications. Thus the developer contained 20 ml buffer, 60 ml hydroquinone and 20 g Acacia with 1 ml silver nitrate added immediately before use. The sections were developed for 10 min at room temperature and after development they were rinsed with distilled water, fixed in 5% sodium thiosulphate for 5 min, washed in tap water for 10 min and counterstained with light haematoxylin and eosin. The presence of mercury in the tissue is demonstrated by the granular deposition of a silver-mercury complex. With this method no mercury could be demonstrated in the kidneys when rats were killed 3 h after a single dose of methylmercury, though their kidneys contained significant amounts of methylmercury. Thus in alkylmercury-treated rats this method shows only inorganic mercury (cleaved in vivo from the carbon bond). For brain and renal histochemistry, one male and one female animal per treatment group was killed 10–12 days after the last of five daily doses. In addition to these six rats, renal histochemistry was also carried out on the kidneys of 12 male rats (four per dose group) sacrificed 3 days after a single treatment.

For the histological examination of brain and dorsal root ganglia rats were perfused through the heart into the aorta with formol-acetic acid (10% formalin, 2% acetic acid) under deep ether anaesthesia. The brain and vertebral column were dissected after a delay of at least 2 h and stored in fixative for 5–7 days. The hind-brain, including the brain stem and cerebellum, was divided in the mid-sagittal plane and both halves embedded in paraffin wax for 5 μm step-serial sectioning. The vertebral column was placed in Gooding and Stewart's decalcifying solution for 2 weeks with three changes. Transverse slices (2 mm thick) were made of the vertebral column to include the cervical (C_4–C_8) and lumbar (T_{13}–L_3) cord enlargements. These were embedded in paraffin wax as composite blocks of the two regions. Step-serial sections (5 μm) were cut to ensure the presence of dorsal ganglia. Brain and spinal cord sections were stained with haematoxylin and eosin, Luxol fast blue and cresyl fast violet.

The severity of granular layer lesions in the depths and crests of the ten cerebellar lobules were scored separately according to a 4-point scale: 1+, few (<2%) pyknotic nuclei; 2+, several (2–10%) pyknotic nuclei; 3+, many (10–50%) pyknotic nuclei 4+, >50% pyknotic nuclei. The degeneration of dorsal root ganglia was also scored on a 3-point scale: 1+ few degenerating cells and Nageotte bodies; 2+, as 1+ but with chromatolytic changes and an increase in the number of satellite cells; 3+, many degenerating cells, large number of Nageotte bodies and satellite cells, with interstitial oedema and cell loss.

D. Assay for organic and inorganic mercury. Total and inorganic mercury and, by difference, organic mercury concentrations were determined by the selective atomic absorption method of Magos (1971) modified to prevent the decomposition of ethylmercury during assay. This was achieved by the reduction of the amount of $SnCl_2$ added to each sample, from 100 mg to 50 μg. Instead of adding $SnCl_2$ in 1 ml suspension to the reaction vessel, it was dissolved in and added with 10 ml 16 N H_2SO_4.

At this concentration the reducing power of tin is not stable and therefore the solution (5.0 mg $SnCl_2$ in 1000 ml 16 NH_2SO_4) must be prepared daily. When standard solutions of methyl- and ethylmercuric chloride were estimated for inorganic mercury by the modified method, methylmercury did not release inorganic mercury at all and the peak given by ethylmercury was 1.0% of the total mercury peak. This 1.0% was probably inorganic mercury contamination. Selected samples in four concentrations ranges were also analysed with a slightly modified version of the liquid gas chromatographic method of Cappon and Smith (1977), and results were compared with the selective atomic absorption method. Table 1 shows that means for organic mercury were slightly but not significantly higher than those given by gas chromatography. Consequently, it is unlikely that the atomic absorption method underestimated organic mercury concentration and consequently could not have over-estimated inorganic mercury concentration.

E. Statistics. The effects of ethylmercury at the two dose levels were compared with the effects of 8.0 mg/kg/day methylmercury. Two tailed multiple comparison procedure (Dunnett 1955) was used to evaluate significant differences ($p<0.05$) in relation to weight loss and mercury concentration, and two-tailed chi-square test or Fisher exact probability test was used to evaluate differences in coordination disorder and histology scores. Scores were arranged in 2×2 contingency tables so that the difference

Table 1. Comparison of the gas chromatographic and atomic absorption determination of organic mercury concentration in brain and blood after the administration of ethylmercury

Sample	Conc. range μg/g	No.	μg Hg/g (mean ± SEM)	
			A.A.	G.C.
Brain	< 12	8	9.8 ± 0.56	9.1 ± 0.7
Brain	12–18	8	15.4 ± 0.61	13.6 ± 0.74
Blood	60–70	8	65.8 ± 1.57	65.4 ± 2.15
Blood	200–400	8	316 ± 19.3	307 ± 19.1

Table 2. Differences between expected body weights (without treatment) and the actual body weights of methyl- and ethylmercuric chloride-treated rats at 0, 5 and 10 days after the last of five daily doses

Compound	Dose in mg Hg/kg	Sex	No.	Relative weight loss in % of expected body weight (mean ± SEM)		
				0 day	5th day	10th day
MeHgCl	8.0	M	24	10.4 ± 0.46	16.3 ± 0.89	18.5 ± 1.34
EtHgCl	8.0	M	22	12.6 ± 0.35*	20.9 ± 0.69*	24.6 ± 1.61*
EtHgCl	9.6	M	23	13.9 ± 0.43*	27.3 ± 0.93*	36.0 ± 1.49*
MeHgCl	8.0	F	18	7.8 ± 0.46	13.8 ± 0.86	20.0 ± 1.34
EtHgCl	8.0	F	18	9.6 ± 0.46*	16.6 ± 1.15	20.8 ± 2.22
EtHgCl	9.6	F	18	9.8 ± 0.45*	19.4 ± 0.98*	28.6 ± 1.74*

* Significantly different from the corresponding MeHgCl-treated groups with the Dunnett t test, $p < 0.05$

between horizontal (or vertical) sums should be as small as possible. The formula used for calculation incorporated correction for continuity (Siegel 1956).

Results

It has been well documented that one of the first toxic effects of methylmercury in rats is depressed weight gain or even weight loss. Table 2 compares weight loss relative to the expected body weight. It can be seen that, based on this criteria, ethylmercury proved to be more toxic than methylmercury. Compared with methylmercury, equimolar doses of ethylmercury caused a significantly larger relative weight loss in male rats at the three selected times, and in female rats at the last treatment day. The higher dose of ethylmercury resulted in consistently greater weight loss in both sexes.

The concentrations of total mercury (the sum of organic and inorganic mercury) and organic mercury was consistently higher in the blood of ethylmercury-treated rats (see Fig. 1) and in the brain (see Fig. 2) and kidneys (see Fig. 3) of methylmercury-treated rats. In blood and brain, but not in kidneys, an increase in the dose of ethylmercury from 8.0 to 9.6 mg Hg/kg/day increased the concentrations of both organic and inorganic mercury. The lack of a consistent increase in the kidney concentration of mercury with dose seems to indicate renotoxicity resulting in a loss of mercury with desquamated cells.

Figures 1–3 also show that in ethylmercury-treated rats inorganic mercury formed a larger proportion of total mercury than in methylmercury-treated rats, but even in the kidneys the concentration of organic mercury remained higher than that of inorganic mercury.

Contrary to weight loss, equimolar doses of ethylmercury caused less severe coordination disorders than methylmercury, though the sum of flailing and crossing scores was significantly less only at 5 days in male and 10 days in female rats (see Fig. 4). This difference was caused by significantly lower flailing scores. Increase in the dose of ethylmercury by 8.0 mg to 9.6 mg Hg/kg/day almost doubled the sum of scores in male, and trebled it in female rats 10 days after treatment when the crossing scores of females were significantly higher than in methylmercury-treated rats.

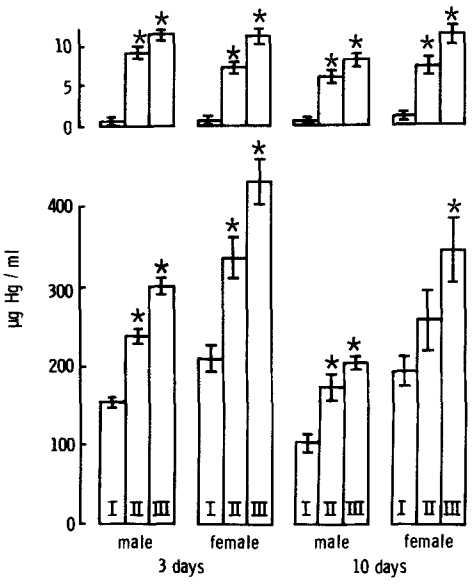

Fig. 1. The blood concentrations of organic *(lower columns)* and inorganic mercury (upper columns) 3 and 10 days after five daily doses of 8.0 mg Hg/kg given as methylmercuric chloride *(Group I)* or ethylmercuric chloride *(Group II)* and 9.6 mg Hg/kg ethylmercuric chloride *(Group III). Asterisks* indicate significant difference (two-tailed Dunnett test, $p<0.05$) from the methylmercury-treated group

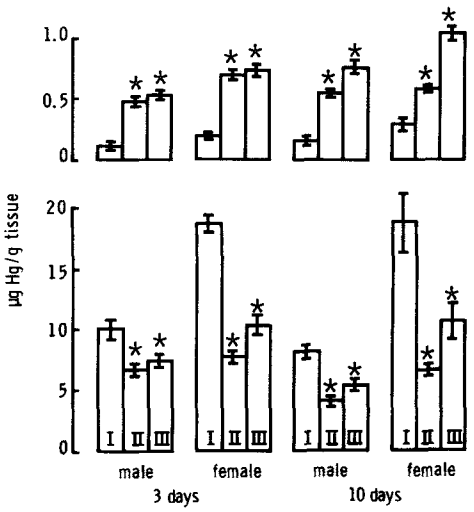

Fig. 2. Brain concentrations of organic and inorganic mercury after five daily treatments with methyl- or ethyl-mercuric chloride. For details see the legend of Fig. 1. Values were corrected to 1.1% blood content (Brown et al. 1976).

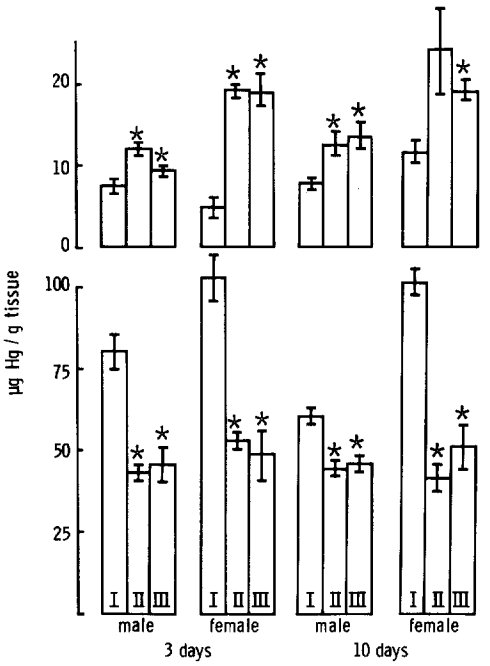

Fig. 3. The kidney concentrations of organic or inorganic mercury after five daily treatments with methyl- or ethylmercuric chloride. For details see the legend of Fig. 1.

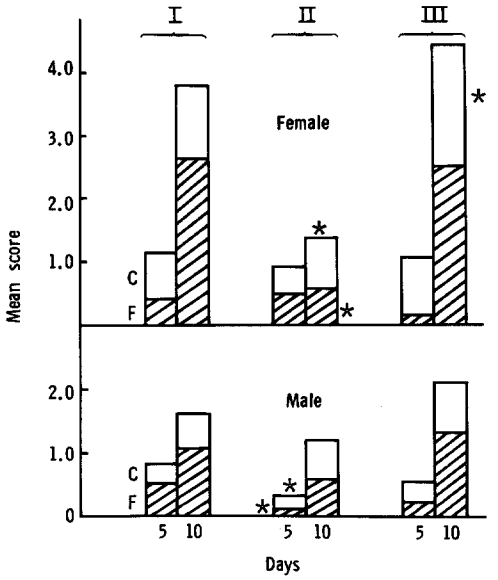

Fig. 4. Coordination disorder scores of male and female rats 5 and 10 days after the last of five daily doses of methyl- or ethylmercuric chloride. *Hatched columns:* flailing reflex; *open columns:* crossing of hind legs. Roman numerals denote the same groups as in Fig. 1. The number of rats are 19 males and 14 females *(Group I)*, 17 males and 14 females *(Group II)*, 19 males and 14 females *(Group III)*. *Asterisks* beside the hatched or open columns indicate significant difference (chi-square test, $p<0.05$) from the corresponding methylmercury mean score, and *asterisks* above columns indicate significant difference for the sum of scores

Table 3 shows that ethylmercuric chloride given in a dose of 8.0 mg Hg/kg/day for 5 days did not damage the granular cells of the cerebellum, while equimolar doses of methylmercury caused granular cell necrosis in six of nine males and in all of the female rats. Some granular cell necrosis was caused by 9.6 mg Hg/kg/day ethylmercury, but the damage was significantly less extensive than in rats given 8.0 mg Hg/kg/day methylmercury. The histochemical test for inorganic mercury did not demonstrate silver-mercury deposits in the granular layer in either methyl- or ethylmercury treated animals but deposits were consistently present in cerebellar roof nuclei and to a smaller extent in Purkinje neurones (see Fig. 5A). In neither the cerebellum nor the brain stem was there any noticeable difference in the density of silver-mercury deposits between animals, with the exception of the male rats treated with methylmercury which had less deposits than the others. Figure 5B shows an area from the brain stem. Contrary to the brain stem and cerebellum, the telencephalon and diencephalon of methylmercury-treated rats had no silver-mercury granules, while in ethylmercury-treated rats the same regions invariably contained mercury, the thalamus more than any other region.

Table 4 shows that both alkylmercuricals damaged the dorsal root ganglia and 9.6 mg Hg/kg/day ethylmercury caused more damage than 8.0 mg Hg/kg/day methylmercury.

Ethylmercury was more renotoxic than methylmercury. Though animals were killed 10–12 days after the last dose, vacuolation and tubular dilation were frequently present, mostly in the P_2 region. Regeneration was also

Table 3. The extent and degree of cerebellar granular layer damage 10–12 days after the last of five daily doses of methyl- or ethyl-mercuric chloride

Compound	Dose in mg Hg per kg	Sex	No. of rats	No. of affected rats	Sum of lobular scores per groups[a]							
					depth				crests			
					0	1+	2+	3+	0	1+	2+	3+
MeHgCl	8.0	M	9	6	56	26	8	0	78	12	0	0
EtHgCl	8.0	M	9	0[b]	90	0	0	0[b]	90	0	0	0[b]
EtHgCl	9.6	M	9	3	76	14	0	0[b]	76	14	0	0[b]
MeHgCl	8.0	F	9	9	7	31	47	5	28	42	19	1
EtHgCl	8.0	F	9	0[b]	90	0	0	0[b]	90	0	0	0[b]
EtHgCl	9.6	F	9	3[b]	71	19	0	0[b]	82	8	0	0[b]

[a] Granular cells in the depths and the crests of each of the ten cerebellar lobules were scored separately in each rat

[b] The number of affected rats or the number of affected lobules are significantly different from the corresponding methylmercury-treated group with the chi-square test

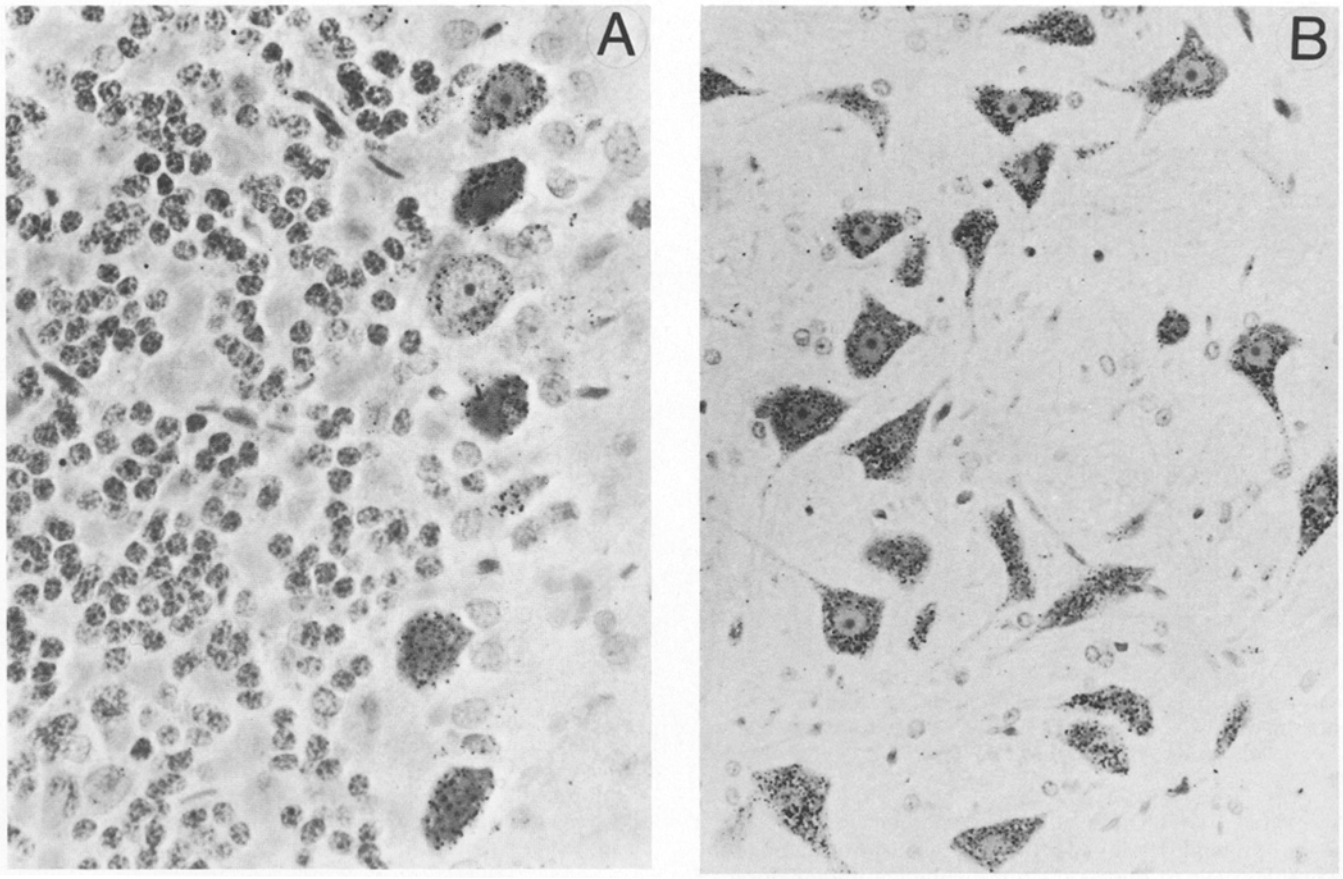

Fig. 5. Silver-mercury deposits in the cerebellum **(A)** and in the nucleus of facial nerve VII **(B)** of an ethylmercury-treated (5 × 8.0 mg Hg/kg) rat killed 10 days after the last treatment day. **A** deposits are in the large Purkinje neurones *(right)* but are absent in the granular layer *(left)*. **B** there are heavy silver-mercury deposits in the neuronal cytoplasm. × 560

present at this time. As Table 5 shows, pathological abnormalities were more frequent and more often extended to P_1 or P_3 regions in ethylmercury-treated than in methylmercury-treated rats. Table 5 also shows that with the exception of male rats treated with 8.0 mg Hg/kg/day ethylmercury, the ethylmercury-treated groups showed more extensive regeneration than methylmercury-treated ones. Fibrosis was seen in only one female rat treated with the higher and in one male rat treated with lower dose of ethylmercury. Metachromasia, pyknotic nuclei and cellular infiltration were seen only in ethylmercury-treated male rats. The extension of damage from P_2 to other regions in ethylmercury-treated rats was in agreement with the presence of the silver-mercury deposits. Both 10–12 days after the last of five daily doses and 72 h after a single dose in ethylmercury-, but not in methylmercury-treated rats, silver-mercury deposits were present not only in the P_2 but also in the P_1 and P_3 region. However, there was no correlation between severity of damage and the density of silver-mercury deposits, because in ethylmercury-treated rats, unlike damage, the localisation of deposits was predominantly in the P_3 region (Fig. 6).

Table 4. Damage in the dorsal root ganglia after the last of five daily doses of methyl- or ethyl-mercuric chloride

Compound	Dose in mg Hg/kg	Days after last dose	Degeneration scores											
			Males $N = 3$				Females $N = 3$				Both sexes $N = 6$			
			0	1+	2+	3+	0	1+	2+	3+	0	1+	2+	3+
MeHgCl	8.0	3–5	1	2	0	0	1	1	1	0	2	3	1	0
EtHgCl	8.0	3–5	2	1	0	0	1	1	1	0	3	2	1	0
EtHgCl	9.6	3–5	0	1	1	1	0	1	1	1	0	2	2	2
MeHgCl	8.0	10–12	0	2	1	0	0	0	1	2	0	2	2	2
EtHgCl	8.0	10–12	1	1	1	0	0	1	0	2	1	2	1	2
EtHgCl	9.6	10–12	0	0	0	3	0	0	0	3	0	0	0	6[a]

[a] Significantly different ($P < 0.05$) from the methylmercury-treated group with Fisher exact probability test

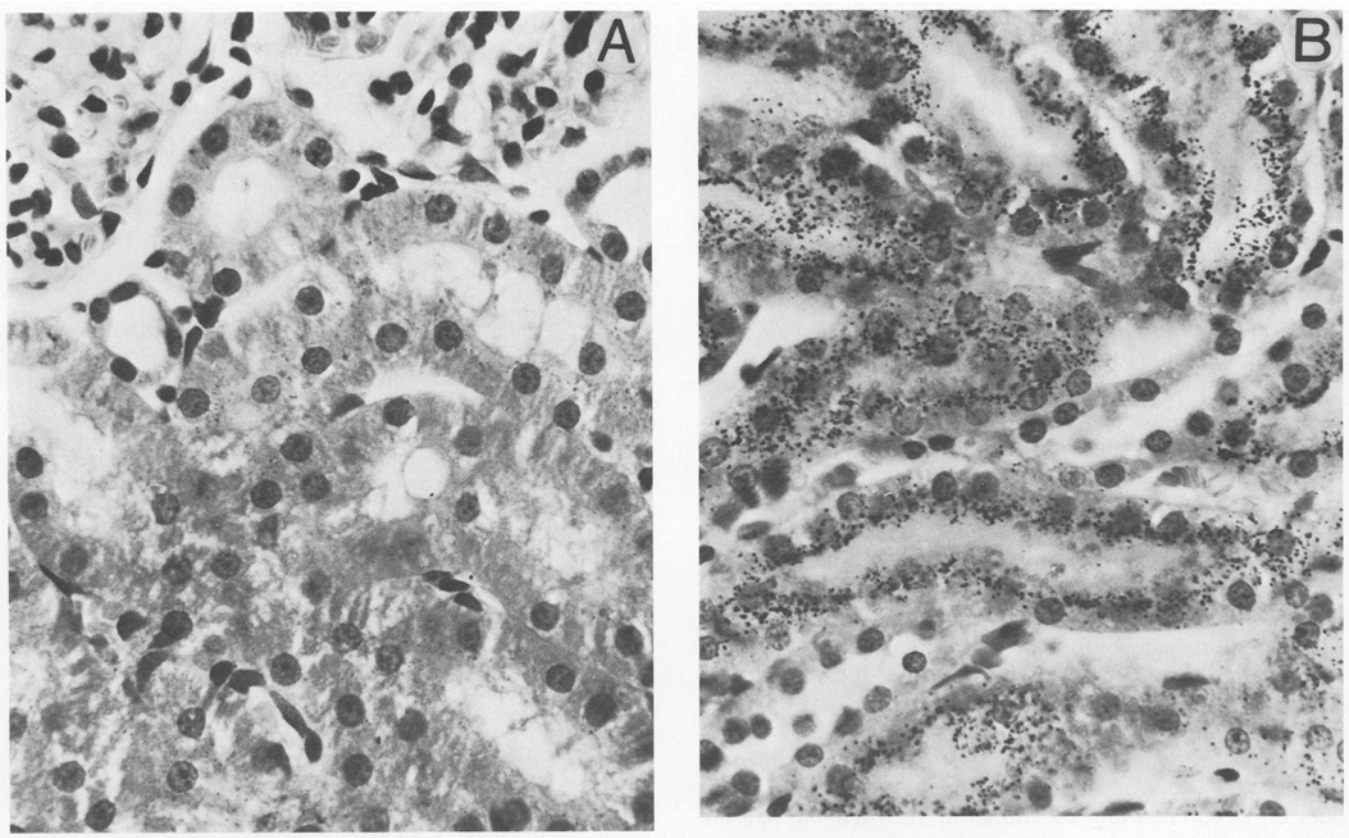

Fig. 6. Silver-mercury deposits in the kidney of an ethylmercury-treated rat 72 h after a single dose of ethylmercury (8.0 mg Hg/kg). **A** light deposits in the P_2 region of the proximal tubules. **B** heavy deposits in the P_3 region (pars recta) of the proximal tubules. × 560

Discussion

The brain accumulates less and kidneys more mercury from ethylmercury than from methylmercury treatment (Suzuki et al. 1963). However, with the prolongation of the exposure period, the difference in the kidney concentration of mercury between the two groups declines (Ulfvarson 1962), indicating that in ethylmercury-treated rats the faster renal accumulation is followed by faster depletion. In fact, as early as 3 days after the last treatment day the kidneys of ethylmercury-treated rats contained less total or organic mercury, though more inorganic mercury, than the kidneys of methylmercury-treated rats. Besides the faster renal depletion of ethylmercury, it is probable that mercury is lost with sloughed tubular cells (Magos 1982a) and the faster decomposition of the ethyl to mercury bond contributed to the difference in organic and inorganic mercury concentrations between ethyl- and methylmercury-treated rats. Increased loss of mercury with more severe renal damage may explain the lack of correlation between the renal concentrations of organic and inorganic mercury and the dose of ethylmercury.

Pathological changes observed in the kidneys 10–12 days after the last treatment day were characterized by the

Table 5. Abnormalities (vacuolation, dilation and regeneration) in the proximal tubular cells 10–12 days after the last of five daily doses of methyl- or ethylmercuric chloride

Compound	Dose in mg/kg/day	Sex	No.	No. of rats with damage		No. of rats with regeneration		
				P_2 region	+ P_1 and/or P_3 region	Slight	Moderate	Extensive
MeHgCl	8.0	M	6	4	1	1	1	1
EtHgCl	8.0	M	6	6	4	1	0	1
EtHgCl	9.6	M	6	6	6[a]	1	2	2
MeHgCl	8.0	F	6	4	0	2	0	0
EtHgCl	8.0	F	6	6	3	0	3	1[a]
EtHgCl	9.6	F	6	6	4[a]	0	2	4[a]

[a] The frequency of abnormalities outside the P_2 region or the frequency of moderate to severe regeneration is significantly different ($P < 0.05$) from the corresponding methylmercury-treated group with the Fisher exact probability test

concurrent presence of vacuolation, dilation, metachromasia, pyknotic nuclei, regenerating cells and fibrosis. Many of these changes are reminiscent of those seen in rats fed on diet containing inorganic mercury or rapidly decomposing phenylmercury (Fitzhugh et al. 1950), and contradict the possibility of acute tubular necrosis followed by postexposure regeneration. The importance of inorganic mercury in these renal abnormalities is indicated by the distribution of damage and inorganic mercury deposits. Mercury deposits, like damage, were principally restricted to the P_2 region in methylmercury-treated rats, whereas both damage and mercury deposits were more widely spread in ethylmercury-treated rats.

In methylmercury-treated rats anorexia resulting in depressed weight gain or weight loss is an indicator of neurotoxicity (Hunter et al. 1949; Magos 1982b). However, when the toxic agent can affect more than one target it is reasonable to suppose that injury to the second target also has a bearing on body weight. In fact, the order of relative weight loss in the three treatment groups, both in males and females, was the same as the order of renotoxicity, whereas the severity of coordination disorders or dorsal root ganglion damage indicated marginally, and granular layer damage significantly higher toxicities for methylmercury than for ethylmercury. However, in the development of coordination disorders, weight loss may have influenced the direct neurotoxic effect. It has been shown previously that lactation moderated the effect of methylmercury on weight loss and coordination disorders but had no effect on dorsal root ganglion or granular layer damage (Magos et al. 1980). In the present experiments, absolute weight loss was always less in male than in female rats. There was no absolute weight loss in male rats treated with 8.0 mg Hg/kg/day methylmercury or ethylmercury, but the initial body weights of female rats decreased by an average of 21.0 g. In male rats dosed with 9.6 mg Hg/kg/day ethylmercury the 36% relative weight loss was equivalent to an average 23.0 g decline in initial body weight, while in female rats the 28% relative weight loss amounted to 38.0 g weight loss. Thus the contribution of weight loss relative to direct neurotoxic effect had to be more important in female than in male rats, and within the same sex more important in ethylmercury-than in methylmercury-treated rats. Another factor may be that, at least in female reats, dorsal root ganglia were damaged by 9.6 mg Hg/kg/day ethylmercury more than by 8.0 mg/kg/day methylmercury. In the present experiments, mercury concentrations were not measured in ganglion cells, but published data indicate that prolonged treatment with $HgCl_2$ can cause focal changes in dorsal root ganglia but, in contrast to methylmercury-treated animals, there is no progression to cell death (Chang and Hartman 1972; Jacobs et al. 1975). Thus mercuric mercury formed extraneously from alkylmercury can contribute to the injury of ganglion cells.

Contrary to dorsal root ganglion damage, the slow decomposition of lipophilic alkylmercurials to inorganic mercury cannot be the cause of neurotoxicity. All ethylmercury-treated rats had more inorganic mercury in their brain than methylmercury ones, but they either had no cerebellar damage (8.0 mg Hg/kg/day) or less damage (9.6 mg Hg/kg/day) than rats given methylmercury (8.0 mg Hg/kg/day). On the contrary, when treatment groups are arranged according to organic or total mercury concentrations, the order of brain mercury concentrations and the order of cerebellar damage are identical. Moreover, the histochemical visualization of inorganic mercury showed no silver-mercury deposits in the granular layer, where the cerebellar damage was largely localized.

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