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Experiments with Different Antidotes in Acute Poisoning by Different Mercury Compounds

Effects on Survival and on Distribution and Excretion of Mercury

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1. Introduction

Since various types of organic and inorganic mercury compounds are distributed in the body and excreted according to entirely different patterns (Swensson, Lundgren and Lindström, 1959a and b; Ulfvarson, 1962; Berlin, 1963; and Berlin and Ullberg, 1963) we considered it of interest to study the effect, of the different anditotes mentioned in the literature, on various mercury compounds. In this connection we studied both the therapeutic effect of these antidotes on survival in acute poisoning and the effect on the distribution of mercury in various organs and on urinary excretion of mercury after administration of small doses of the different mercury compounds.

2. Survey of Literature

In the following survey of the literature we shall deal only with those antidotes which we ourselves have studied in the experimental investigation. Since it is quite evident that the effect of a certain antidote depends upon the form in which the mercury was administered we have arranged the report according to the relevant mercury compounds.

2.1. Dimercaptopropanol, BAL

Waters and Stock (1945) suggested the use of BAL as an antidote against poisoning by mercury salts.

2.1.1. Poisoning by Metallic Mercury

The data on the effect of BAL in poisoning by metallic mercury diverge to a very great extent in the extremely comprehensive literature.

2.1.1.1. Acute Poisoning. Treatment with BAL has been tested by Burke and Quagliana, 1963; King, 1954; Matthes, Kirschner, Yow and Brennan, 1958 with uncertain results. In subacute, experimental poisoning: Biondi and Guarino,

1956, and GUARINO and BIONDI, 1957 observed, if anything, deterioration in connection with BAL treatment.

2.1.1.2. Chronic Poisoning. Treatment with BAL was tested by OCHOTA, 1950; WOODCOCK, 1958; TAMIR, BORNSTEIN, BEHAR and CHWAT, 1964; and BRUGSCH, 1965, who did not find that this treatment produced any therapeutic effect. Nor has any effect of the treatment been observed insofar as mercury excretion in the urine has been studied. BELL, GILLILAND, and DUNN (1955) consider that they obtained a favourable therapeutic effect in one case, but there was no increase in the excretion of mercury; whereas LOB and DESBAUMES (1965) maintained that they had noted a certain increase in urinary mercury excretion, but were unable to observed any therapeutic effect. BALDI (1950) reported a therapeutic effect. Clinical improvement and simultaneous increase in mercury excretion in the urine were stated to have occurred by ALAJOUANINE, CASTAIGNE, CAMBIER and FOURNIER, 1957; HADENGUE, BARRÉ, MANSON, LE BRETON and CHARLIER, 1957; SPEIRS, 1959. SPEIRS stated that the increase of excretion of mercury was significant and that "It is difficult to believe that this small increase lasting only the 10 days of the treatment could make a significant difference to the course of the disease".

Thus the data are very contradictory, which can perhaps be explained by the fact that in most of the publications the discussion is based on observations of a single or of only a few cases. The initial situation, when treatment was introduced, has varied very widely and, consequently, it is difficult to draw any general conclusions. BATIGELLI (1960) is sceptical with regard to the therapeutic effect.

2.1.1.3. Pink Disease. In this disease, where in many cases urinary excretion of mercury is increased, treatment with BAL has been tried with varying results. Certain authors stated that they obtained a clinical effect, with regression of the symptoms, whereas others did not observed these results. The same applies to the data on the effect of BAL treatment on the urinary excretion of mercury (ANDERSEN, 1951; FISCHER and HODES, 1952; HOLZEL and JAMES, 1952; WARKANY and HUBBARD, 1953; CHEEK, 1953).

2.1.2. Poisoning by Inorganic Mercury Salts

2.1.2.1. Acute Poisoning. The life-saving effect of the early application of BAL treatment is generally attested on the basis of experimental and clinical experiences (BRAUN, LUSKY and CALVER, 1946; LONGCOPE, 1946; GILMAN, ALLEN, PHILIPS and JOHN, 1946; LONGCOPE and LUETSCHER, 1946; LUETSCHER and LONGCOPE, 1946; STOCKEN, 1947; SULZBERGER and BAER, 1947; ROSKAM, HEUSGHEN, RENARD and SWALUE, 1948; BATSON and PETERSON, 1948; GINZLER, 1949; KANEE and STOFFMAN, 1949; ZEGLIO, 1949; LAFARGUE, DOUTRE and DAVID-CHAUSSE, 1949; FITZSIMMONS and KOZELKA, 1950; MACFARLAND, 1950; LEVY, MOIR and MILLER, 1950; ADAM, 1951; LONGCOPE, 1952; WILSON, THOMSON and HOLZEL, 1952; MONTUSCHI, 1953; GODET, 1954; MASUI, 1957; ALAJOUANINE, CASTAIGNE, CAMBIER and FOURNIER, 1957; BELONZHKO, 1958; GLÖMME and GUSTAVSON, 1959; ROSE, CHEN and HARRIS, 1964).

Some authors assert that BAL treatment produces an increase in the urinary excretion of mercury (ADAM, 1951; LONGCOPE, 1952; BELL, GILLILAND and DUNN, 1955). LONGCOPE and LUETSCHER (1946) found large amounts of mercury in the feces during treatment with BAL.

In animal experiments ULFVARSON (1963) showed an increase in the urinary excretion of mercury in animals which, after adminstration of mercuric nitrate,

were treated with BAL. He also demonstrated a certain redistribution of mercury between the organs, and that the mercury content was substantially reduced, especially in the kidneys. ADAM (1951) reported similar results, whereas FITZSIMMONS and KOZELKA (1950) stated that they found a decrease in the urinary excretion of mercury and an increase in the fecal excretion. FITZSIMMONS and KOZELKA (1950) and BERLIN and LEWANDER (1964) observed a similar redistribution following BAL treatment.

LIVINGSTONE and PRICE (1950) reported that BAL treatment had a favourable effect on salyrgan poisoning, and BORGHGRAEF and PITTS (1956) asserted that BAL treatment, after administration of chlormerodrin, increased the urinary excretion of mercury and caused a certain redistribution, with a reduction of the mercury content in the kidneys and an increase in the other organs.

2.1.3. Poisoning by Alkyl Mercury Compounds

It may be appropriate to point out that technical products of alkyl mercury compounds are not pure, but contain different types of mercury compounds as impurities, organic as well as inorganic. This may explain some of the inconsistencies in the results reported in different papers.

2.1.3.1. Acute Poisoning. In a case of severe poisoning, which was running a lethal course, HÖÖK, LUNDGREN and SWENSSON (1954) were unable to show that treatment with BAL had either a therapeutic effect or influenced the excretion of mercury. GLÖMME and GUSTAVSON (1959) did not observe any therapeutic effect in animal experiments. ULFVARSON (1963) did not find any increase in the excretion of mercury in animal experiments as a result of BAL treatment. He observed, however, a certain redistribution of mercury, so that the central nervous system in the animals treated had a somewhat higher mercury content than that of the animals which had been given only alkyl mercury compounds without BAL treatment. BERLIN et al. (1964) reported similar results. This seems to indicate the necessity of taking particular care when applying BAL treatment in cases of acute poisoning by alkyl mercury compounds.

2.1.3.2. Chronic Poisoning. AHLBORG and AHLMARK (1949) reported that they had observed a regression of symptoms when treating a case of alkyl mercury poisoning with BAL; and that during treatment there was a great increase in the urinary excretion of mercury. ENGLESON and HERNER (1952) also stated that BAL treatment applied in such a case produced increased urinary excretion of mercury. The increase which was reported, however, is hardly larger than the normal day to day variations in excretion. JALILI and ABBASI (1961) used BAL treatment in a number of cases of poisoning and summarize their experience as follows: "Our general impression is that it did not influence the course of the disease". They state, however, that in one or two cases, but not in several, they thought they noted a certain improvement during treatment. HÖÖK, LUNDGREN and SWENSSON (1954) showed that in one case there was a certain increase in mercury excretion and a certain regression of the residue symptoms, when BAL treatment was given a long time after the actual exposition; in another case there was no effect.

2.1.4. Poisoning by Alkoxyalkyl and Phenyl Mercury Compounds

Here only a few reports are available. In animal experiments ULFVARSON (1963) has shown that, after the administration of a phenyl mercury compound, treatment with BAL produces a great increase in the urinary excretion of mercury. The same treatment, following administration of a methoxyethyl mercury compound

gives a somewhat lower increase in the urinary excretion of mercury. He demonstrated also a redistribution of mercury as a result of the treatment. GOLDWATER, LADD, BERKHOUT and JACOBS (1964) did not obtain any definite increase in excretion due to BAL treatment in a case of acute poisoning by phenyl mercury acetate.

2.2. Ethylene Diamine Tetraacetic Acid, EDTA

EDTA has been tested as an antidote against poisoning by different types of mercury compounds.

2.2.1. Poisoning by Metallic Mercury

2.2.1.1. Acute Poisoning. BIONDI and GUARINO (1956) and GUARINO and BIONDI (1957) observed increased urinary secretion of mercury as a result of EDTA treatment of rabbits that had inhaled mercury vapours as compared with animals that inhaled mercury but received no treatment.

2.2.1.2. Chronic Poisoning. In therapeutic experiments with chronic mercurialism, BELL, GILLILAND and DUNN (1955) found that the administration of EDTA diminished the urinary excretion of mercury. HADENGUE, BARRÉ, MANSON, LE BRETON and CHARLIER (1957) did not observe any effect on the excretion of mercury or any therapeutic effect. In one case WOODCOCK (1958) seems to have obtained an increase in excretion and clinical improvement in connection with EDTA treatment.

2.2.2. Poisoning by Inorganic Mercury Salts

2.2.2.1. Acute Poisoning. TACHI and NIIMURA (1955) stated that they had obtained increased urinary excretion of mercury as a result of EDTA treatment. KOBAYASKI (1959) also observed an increase in urinary excretion of mercury when applying EDTA treatment, whereas fecal excretion was not affected. On the other hand, TURRIAN, GRANDJEAN, BÄTTIG and TURRIAN (1956) did not obtain any increase in excretion. In animal experiments MASUI, 1957; TURRIAN, GRANDJEAN, BÄTTIG and TURRIAN, 1956; GLÖMME and GUSTAVSON, 1959 were unable to show that EDTA treatment produced a life-saving effect. ULFVARSON (1963) did not find, in his experiments, any increase in excretion, but a certain redistribution of mercury, as a result of EDTA treatment.

2.2.3. Poisoning by Organic Mercury Compounds

HOLM (1954) studied in swine different alkyl and aryl mercury compounds and considered that he was able to observe increased mercury excretion in connection with EDTA treatment. He regarded this as due only to the purely diuretic effect of EDTA. Moreover, he believed that the mercury complex was as toxic as the mercury compound and concluded that "Calcium versenate is of no value in treating swine mercurialism". GLÖMME and GUSTAVSSON (1959) did not find that EDTA had any therapeutic effect in experimental poisoning with alkyl mercury compounds. ULFVARSON (1963) showed that EDTA treatment, following the administration of alkyl or phenyl mercury compounds, did not cause any increase in excretion, but that such increase was observed when EDTA treatment was applied after administration of methoxyethyl mercury compounds. He showed, however, that EDTA treatment led to a certain redistribution of mercury for all the mercury compounds mentioned.

2.3. Sodium Formaldehyde Sulfoxylate, Rongalite C

Rongalite C has been used only in cases of acute poisoning by inorganic mercury compounds.

ROSENTHAL (1933) showed that Rongalite C is an effective antidote against experimental poisoning by mercuric chloride, if treatment is introduced within 20—25 min after administration of the sublimate. When applied after longer intervals the substance was completely ineffective. ROSENTHAL introduced the substance as an antidote in cases of clinical poisoning and considered that he had obtained very favourable results (1934 and 1935). MONTE and HULL (1934), however, were unable to obtain the same favourable result in cases of clinical poisoning. BROWN and KOLMER (1934) maintained that Rongalite C had to be administered very quickly before the renal epithelium was damaged. This greatly restricts the applicability of the substance in cases of clinical poisoning. The treatment is of value if it can be introduced a few minutes after the poison has been taken. MODELL, GOLD, WINTHROP and FOOT (1937) considered that they had also obtained favourable results in cases of clinical poisoning, provided that treatment was applied very quickly. MONTE and HULL (1940) are of the opinion that Rongalite C treatment has to be applied almost immediately after the administration of the mercury compound in order to obtain a therapeutic result. This is also the opinion of WOLPAW and ALBERS, 1942; CHEYMOL and LECHAT, 1947; BROOKES and JACOBS, 1958; MUNOZ, 1935. STOCKEN (1947) considered that there was only a slight therapeutic effect in animal experiments; and ANTONIO (1949) did not obtain an essentially life-saving effect in animal experiments. SOLLMAN (1957) emphasized that the drug had to be administered very quickly in order to be effective. Finally, this is also recommended by FABRE and TRUHAUT (1960).

2.4. Dimethyl Cysteine, Penicillamine

HADENGUE, FABIANI and QUEUILLE (1950) showed that, on administration of calomel, urinary excretion of mercury was greatly increased when penicillin treatment was simultaneously given. It was assumed that this might be caused by the penicillin metabolite, penicillamine.

2.4.1. Poisoning by Metallic Mercury

PAGNOTTI, BRUGSCH and ELKINS (1960) were unable to observe that the treatment affected the symptoms in chronic mercurialism; whereas SMITH and MILLER (1961) considered that they had noticed improvement. They were unable to demonstrate any increase in the excretion of mercury. KAZANTZIS, SCHILLER, ASSCHER and DREW (1962) were unable to show, in a case of nephrosis in connection with exposure to metallic mercury, any effect on the symptoms or any increase in excretion of mercury when penicillamine therapy was applied. The same results were reported by TAMIR, BORNSTEIN, BEHAR and CHWAT (1962). In a case of pink disease, HIRSCHMAN, FEINGOLD and BOYLEN (1963) reported increased urinary excretion of mercury when N-acetyl-DL-penicillamine treatment was given.

2.4.2. Poisoning by Inorganic Mercury Salts

APOSHIAN (1958 and 1959) and APOSHIAN and APOSHIAN (1959) demonstrated a very favourable therapeutic effect in experimental poisoning by mercuric nitrate. It was also shown that D-penicillamine was more effective than L-penicillamine, and that N-acetyl-DL-penicillamine is the most effective.

2.5. Ascorbic Acid

Ascorbic acid was stated by MARIN (1941) to be an effective antidote in animal experiments if it was injected intravenously within 10 min of parenteral administration of mercuric nitrate. He stated moreover that "A mixture of $HgCl_2$ and ascorbic acid in the molecular ratio of 1:2 is not toxic since all of the $HgCl_2$ is reduced to HgCl or Hg". This conception, also with regard to the active mechanism, is upheld by ŠUŠCIC and MAKSIMOVIC (1956). WAUTHERY and WAUTHERY (1947) considered that premedication with ascorbic acid had, in animal experiments, a certain protective effect in poisoning by mercury /I/ cyanide. FROMMEL and LOUTFI (1944), on the other hand, were unable to observe that ascorbic acid had, in animal experiments, any therapeutic effect in poisoning by sublimate, whereas FRANK (1962) stated that a surplus of ascorbic acid had a certain protective effect.

2.6. Thioctic Acid

BONI, REDUZZI, BILE and CALARO (1955) stated that thioctic acid had a therapeutic effect on experimental poisoning with inorganic mercury salts; REDUZZI (1955), however, was unable to confirm this. HETOMI, FUKE, WATANABE, HONDA and KUMADA (1958), and GRUNERT (1960) reported a favourable effect in the form of a higher survival rate.

2.7. Thiomalic Acid

2.7.1. Poisoning by Metallic Mercury

GODET (1954) considered that he had obtained favourable results in the treatment of chronic mercurialism, whereas WORMS, WEILL-HEULOT and TUBIANA (1948) did not observe any definite effect.

2.7.2. Poisoning by Inorganic Mercury Salts

MEIDINGER (1947 and 1949) showed that thiomalic acid had a therapeutic effect in poisoning by inorganic mercury salts and he considered that the effect was greater than that after treatment with BAL. This was confirmed by THIRS and PELLERAT (1949), who stated that thiomalic acid was more effective than BAL and Rongalite C. Similar results were reported by KOSTYGOV (1958).

2.8. Thioacetamide

LIPIEC (1965) states that thioacetamide has a therapeutic effect in experimental poisoning by inorganic mercury salts.

2.9. Para-Amino Salicyclic Acid, PAS

PAS according to its structure should be able to chelate metal ions and has therefore been included in this study.

3. Own Investigations

3.1. Effect on Survival

3.1.1. Design of the Experiments

3.1.1.1. Mercury Compounds Studied. As is evident from the survey of the literature the experience gained hitherto with regard to therapy

refers mainly to poisoning by inorganic salts, whereas investigations into the effect of antidotes against poisoning by different organic compounds occur much less frequently. In view of the fact that various types of mercury compounds are being increasingly used as fungicides and preservatives in agriculture and horticulture, and in the paper-pulp, leather, and paint industries, and since these substances are both highly toxic and their behaviour in the organism is quite different from that of the inorganic salts, in this investigation we have studied the different types of organic mercury compounds that are relevant in this connection. Moreover, we have taken mercuric nitrate as our substance for comparison. The following mercury compounds have been studied:

1. Mercuric nitrate.
2. Methyl mercury hydroxide.
3. Methoxyethyl mercury hydroxide.
4. Phenyl mercury hydroxide.

3.1.1.2. Antidotes Studied. The antidotal effects of the substances mentioned below were tested in repeated doses with the stated amount per dose:

1. Dimercaptopropanol, BAL, 25 mg/kg body weight.
2. Ethylenediaminetetraacetic acid-Na_2-Ca, EDTA-Na_2-Ca, 100 mg/kg body weight.
3. Dimethylcysteine, D-penicillamine, 25 and 65 mg/kg body weight.
4. Ascorbic acid, 250 mg/kg body weight.
5. Thioctic acid, 50 mg/kg body weight.
6. Formaldehyde sodium sulphoxylate, Rongalite C, 125 mg/kg body weight.
7. Thiomalic acid, 50 mg/kg body weight.
8. Thioacetamide, 10 mg/kg body weight.
9. Paraamino salicylic acid, PAS, 200 mg/kg body weight.

3.1.1.3. Experimental Animals. Males of a homogeneous strain of Sprague-Dowley rats were used throughout in the experiments. At the beginning of the experiments the animals weighed about 200 g. They were kept under standardized conditions during the experimental period.

3.1.1.4. Experimental Technique. Aqueous solutions of the mercury compounds were injected subcutaneously in a single dose, which, as far as possible, was so adjusted as to cause a mortality of some 80—90 per cent in the control group of untreated animals. Large groups of animals were injected with one and the same substance; subsequently, they were randomly divided into different subgroups, which were treated with the various antidotes or served as control groups. By this means systematic differences in dosage between the various groups were avoided.

Therapy was carried out by intraperitoneal injections of the stated dose twice daily for 5 days. In one series of experiments administration of the antidotes was begun within 10 min after the injection of the mercury compound; in another series the interval was 4 hours.

The number of surviving animals was recorded at the end of every 24-hour period after injection during 2—3 weeks. A long observation time was necessary in experiments with methyl mercury compounds.

3.1.2. Results

3.1.2.1. Mercuric Nitrate (Table 1) in a dose of about 10 mg Hg/kg body weight caused a mortality of 100 per cent within 4 days in the untreated control group. Thioctic acid, EDTA, penicillamine, ascorbic acid, and Rongalite C had no life-saving effect. Only BAL had a distinct therapeutic effect when this dose of mercury was administered.

With a dose of 7.5 mg Hg/kg body weight mortality in the control group was reduced to 80—90 per cent, and in a later experiment it was only 60 per cent. With this dose of mercury not a single animal died in the groups that were treated with BAL or Rongalite C when treatment

Table 1

Accumulated mortality within 14 days after subcuteneous injection to rats of mercuric nitrate in an amount corresponding to the amount of mercury stated in different columns. Treatment as described in text. Number of deaths/number of animals injected

	Therapy started within 10 min				Therapy started after 4 hours		
	10	7.5	7.5	7.5	7.5	7.5	7.5
Controls	10/10	8/10	8/10	9/10	6/10	9/10	8/10
BAL	*5/10*	*0/10*	—	—	*0/10*	—	—
EDTA	—	10/10	—	—	10/10	—	—
D-Penicillamine:							
low dose	10/10	9/10	—	—	6/10	—	—
high dose	—	—	*3/10*	—	—	—	*4/10*
Ascorbic acid	10/10	—	—	—	—	—	—
Thioctic acid	10/10	*1/10*	—	—	7/10	—	—
Rongalite C	10/10	*0/10*	—	—	5/10	—	—
Thiomalic acid	—	—	—	10/10	—	7/10	—
Thioacetamide	—	—	—	9/10	—	8/10	—
PAS	—	—	—	10/10	—	—	8/10

was introduced within 10 min. The higher dosage of penicillamine had a therapeutic effect but not the lower. Thioctic acid also showed a distinct therapeutic effect for this dose of mercury when treatment was introduced immediately. On the other hand, the remaining antidotes did not have any life-saving effect.

When treatment was introduced only 4 hours after the administration of mercury a somewhat different picture was obtained. Also in this case BAL and the higher dosage of penicillamine had a clear life-saving effect, whereas the other antidotes had no observable action. The animals that were treated with EDTA died sooner than the animals in the remaining groups, including the control group.

Table 2. *Accumulated mortality within 21 days after subcutaneous injection to rats of methyl mercury hydroxide in a dose corresponding to the amounts of mercury stated in different columns. Tretament as described in text. Number of deaths/number of animals injected*

	Treatment startet within 10 min after injection of mercury compound				Treatment started 4 hours after injection of mercury compound		
	40	50	40	40	50	40	40
Controls	4/10	10/10	5/10	4/10	10/10	5/10	4/10
BAL	2/10	10/10	—	—	8/10	—	—
EDTA	6/10	—	—	—	—	—	—
D-Penicillamine:							
low dose	7/10	10/10	—	—	10/10	—	—
high dose	—	—	5/10	—	—	4/10	—
Ascorbic acid	1/10	10/10	—	—	10/10	—	—
Thioctic acid	4/10	10/10	—	—	10/10	—	—
Rongalite C	—	10/10	—	—	10/10	—	—
Thiomalic acid	—	—	—	6/10	—	—	6/10
Thioacetamide	—	—	—	6/10	—	—	2/10
PAS	—	—	—	3/10	—	—	2/10

3.1.2.2. Methyl Mercury Hydroxide (Table 2) given in a dose of 40 mg mercury/kg body weight produced in the untreated control groups a mortality of only 40 per cent. None of the antidotes tested showed any manifest life-saving effect.

When a dose of 50 mg Hg/kg body weight was administered the mortality in the control group was 100 per cent. None of the antidotes tested had a life-saving effect.

Thus, in acute poisoning by the alkyl mercury compound none of the antidotes tested produced a therapeutic effect.

3.1.2.3. Phenyl Mercury Hydroxide (Table 3) in a dose of 30 mg Hg/kg body weight caused a mortality of 80—100 per cent in the untreated control groups. Immediate treatment with BAL, Rongalite C, and thioctic acid seems to have a therapeutic effect, whereas the other antidotes were inactive. If the dose was increased to 40 mg Hg/kg body weight the mortality in the control group was 100 per cent within 5 days.

Table 3. *Accumulated mortality within 14 days after subcutaneous administration to rats of phenyl mercury hydroxide in a dose corresponding to the amounts of mercury stated in different columns. Treatment as described in text. Number of deaths/number of animals injected*

	Treatment started within 10 min. after injection of mercury compound			Treatment started 4 hours after injection of mercury compound	
	40	30	30	30	30
Controls	10/10	9/10	8/10	10/10	8/10
BAL	7/10	*2/10*	—	*3/10*	—
EDTA	10/10	—	—	—	—
D-Penicillamine, low dose	10/10	7/10	—	*4/10*	—
Ascorbic acid	10/10	—	—	—	—
Thioctic acid	9/10	*3/10*	—	7/10	—
Rongalite C	7/10	*4/10*	—	8/10	—
Thiomalic acid	—	—	10/10	—	5/10
Thioacetamide	—	—	9/10	—	8/10
PAS	—	—	6/10	—	*3/10*

Here it is possible that BAL and Rongalite C have some life-saving effect with a 30 per cent survival.

If BAL treatment was applied 4 hours after administration of the mercury compound there was still a distinct therapeutic effect. Penicillamine, too, had a life-saving effect when treatment was started 4 hours after the administration of the mercury compound. As we had no favourable effect when the treatment was started immediately, we think that the positive effect in the other series is due to chance. In this experiment there was also increased survival when PAS was used. No manifest effect was obtained with any of the other antidotes.

3.1.2.4. Methoxyethyl Mercury Hydroxide (Table 4) in a dose of 40 mg Hg/kg body weight caused a mortality of 100 per cent in the control group. None of the antidotes tested had any life-saving effect when this dose of the mercury compound was given. The animals which were treated with BAL died of acute spasms in direct connection with the second injection of BAL. For this reason experiments with BAL treatment were not continued for this form of mercury poisoning.

When a dose of 25 mg Hg/kg body weight was given, immediate treatment with Rongalite C had a life-saving effect. If treatment was first introduced after 4 hours penicillamine had a life-saving effect when given in a low dose but not in a high dose. This seems not reasonable and we therefore think that the favourable figure in the first case is due to chance. All other antidotes tested were without effect.

Table 4. *Accumulated mortality within 14 days after subcutaneous injection to rats of methoxyethyl mercury hydroxide in a dose corresponding to the amount of mercury stated in different columns, mg/kg of body weight. Treatment as described in text. Number of deaths/number of animals injected*

	Treatment started within 10 min after injection of mercury compound				Treatment started 4 hours after injection of mercury compound	
	40	25	25	25	25	25
Controls	10/10	9/10	10/10	10/10	9/10	10/10
BAL	10/10*	—	—	—	—	—
EDTA	10/10	—	—	—	—	—
D-Penicillamine,						
low dose	10/10	7/10	—	—	4/10	—
high dose	—	—	7/10	—	—	10/10
Ascorbic acid	10/10	—	—	—	—	—
Thioctic acid	10/10	9/10	—	—	10/10	—
Rongalite C	8/10	*4/10*	—	—	8/10	—
Thiomalic acid	—	—	—	8/10	—	9/10
Thioacetamide	—	—	—	10/10	—	10/10
PAS	—	—	—	8/10	—	10/10

* All animals died acutely following the second injection of BAL.

3.2. Effects on Distribution and Excretion of Mercury

3.2.1. Design of the Experiments

3.2.1.1. Mercury Compounds Studied. Compounds of the same types as those mentioned in the preceding section were studied. In order to follow the distribution and excretion of mercury we used compounds labelled with the radioactive isotope Hg-203. Labelling and measuring of the mercury compounds, and preparation of the samples were made as described in previous communications (SWENSSON, LUNDGREN and LINDSTRÖM, 1959a and b; ULFVARSON, 1962).

Radioactive mercuric oxide was obtained from AB Atomenergi, Stockholm. Initial specific activity was usually about 20 mCi/g of mercury. The mercuric oxide was dissolved in dilute nitric acid 1:10. The excess acid was neutralized up to a pH of about 1. A higher pH would result in precipitation of the oxide. The active methyl mercury and methoxyethyl mercury compounds were prepared by adding, to the solution of mercuric nitrate, inactive solutions of methyl mercury hydroxide and methoxyethyl mercury hydroxide respectively, the proportion of active to inactive mercury being 1:1. After a reaction time of 24 hours the inorganic mercury ion was precipitated by the addition of sodium hydroxide to pH 10.

The phenyl mercury compound was labelled by dissolving phenyl mercury acetate in glacial acetic acid. This solution was added to the active mercuric nitrate solution so as to obtain the same proportion of active to inactive mercury as that stated previously. Precipitation of the inorganic mercury was obtained in the same way as with the other compounds. Concentrations of the active solutions were controlled by analyzing, after digestion, by the colorimetric, dithizone method

(JOHANSSON and UHRNELL, 1955). The solutions were diluted to a suitable concentration before injection.

3.2.1.2. The Antidotes Studied were the same as in the preceding section.

3.2.1.3. As in the foregoing section, the *experimental animals* were male rats of a uniform Sprague-Dowley strain.

3.2.1.4. Experimental Technique. Aqueous solutions of the mercury compounds were intravenously injected after severing the skin on one of the back legs during shallow ether anesthesia.

The skin was sutured. The concentration of the solution was so adjusted that the amount of mercury injected was always contained in 0.5 ml. The distribution of the animals into different groups for treatment with various antidotes and into control groups was carried out in the same way as described in the preceding section.

The antidotes were administered by intraperitoneal injection twice daily for three days, with the first injection given immediately after administration of the mercury compound.

This part of the investigation comprises four different experiments. In all the experiments the animals that received the same treatment were kept in one and the same cage, and the urine and feces of all the animals were collected together for each 24-hour period. In the first three experiments the animals in the control group were kept in the same way in one cage, but in the fourth experiment each control animal was kept in a separate cage and, consequently, excretion could be determined for each individual.

In *experiment 1* the mercurials injected corresponded to 10 μg of mercury per animal, except for methyl mercury hydroxide, which corresponded to 20 μg of mercury per animal. D-penicillamine and Ca-Na_2-EDTA were given as a water solution, 100 mg/kg and 150 mg/kg respectively in each injection and BAL in peanut oil solution in a dose of 25 mg/kg.

In *experiment 2* only methoxyethyl mercury hydroxide was used. It was injected in an amount corresponding to 100 μg of mercury per animal. The amount of D-penicillamine given each time was 100 mg/kg and that of EDTA-Na_2-Ca 250 mg/kg.

In *experiment 3* the mercurials were injected in amounts corresponding to 100 μg of mercury per animal. As antidote, ascorbic acid was given, 250 mg/kg each time.

In *experiment 4* the mercurials were injected in amounts corresponding to 100 μg of mercury per animal. The antidotes were given in the following amounts each time:

Thioctic acid 50 mg/kg as a 5 per cent solution in a 3 per cent sodium bicarbonate solution in water.

Rongalite C, 125 mg/kg as a 5 per cent solution in water; thiomalic acid, 50 mg/kg as a 2 per cent solution in water; thioacetamide, 10 mg/kg as a 1 per cent solution in water; PAS, 200 mg/kg, as a 4 per cent solution in 3 per cent sodium bicarbonate in water.

3.2.1.5. Animals killed on the fourth day and organs removed for analysis.

3.2.1.6. Preparation of Samples. In experiment 1, each organ from a group of animals was bulked and homogenized with a glass rod in a glass bottle. Two grams of each bulk were weighed into a polyethylene tube used for measurement. In experiments 2, 3, and 4, each organ from every animal was analyzed separately. Whole organs or parts of an organ were put directly into the weighed polyethylene tube. The tubes were sealed, weighed, and then analyzed for radioactivity.

In those cases where, after removing the organs, the rest of the body was analyzed, we used the technique described earlier (ULFVARSON, 1962). The carcass was digested in boiling 40 per cent sodium hydroxide for about 30 min. In this way all the organic material was destroyed and samples could be taken from the clear solution.

Faeces and urine were collected on filter papers on the bottom of the cage below a wire net on which the animals were kept. The filter papers were changed each day. Feces were separated from the papers containing urine components. Feces and paper were ground, in dry state, in a Turmix mill. A certain volume of the homogenized sample thus obtained was transferred to a polyethylene tube for measuring the radioactivity.

3.2.1.7. Measurement of Radioactivity. γ-counting, with scintillation technique, was used as previously described (ULFVARSON, 1962). A well-type crystal was employed (Philips). The well was 20 mm in diameter and 50 mm deep. The samples were contained in closed polyethylene tubes which fitted precisely in the well of the crystal.

3.2.1.8. Correction for Geometrical Deviations in the Well Crystal. In experiment 1, where the organs were bulked and homogenized, the volumes in the polyethylene tubes were kept constant. Variations due to the geometrical factor were thus eliminated. In experiments 2, 3, and 4 where whole organs or pieces of organs were put directly into the tubes the different samples had different volumes. Since the geometrical influence on the rate of scintillation in the well crystal might be considerable a correction had to be made. This was done as follows. A droplet of a $^{203}Hg/NO_3/_2$-solution was put on the bottom of a polyethylene tube. The decrease in the rate of the scintillations, when the solution was diluted stepwise with distilled water, was observed. The activity of the content of the tube was obviously the same all the time, the only variable being the volume. Correction factors were calculated from the data obtained, and plotted against the volume of the solution, so as to give a correction curve.

When the measurements of the organs were corrected, the weight, rather than the volume, of the organ was used; it was assumed that the specific weight of the organs was 1 and that the tubes were perfectly packed. The error introduced by this approximation may be regarded as negligible. Although the corrections may be considerable, the coefficient of variation, in double determinations of different amounts of the same organ, is only a few per cent after correction.

3.2.1.9. Statistical Analysis. The experiments reported on here were not planned and carried out at one time. Especially experiment 1 should be regarded as an introductory experiment. Here, the organs of different animals were taken together and analyzed as a whole. The results of these analyses were treated in what follows as mean values. Double determinations were made in connection with these composite samples. The standard deviations for these determinations can be used as a measure of such variations as depend, for example, upon the inhomogenity of the sample, and errors in weighing and analysis. For low concentrations of mercury statistical errors in scintillation counting are probably dominant; for high concentrations it is likely to be errors due to difficulties in homogenizing the organs. Since radioactivity decreases, the error in scintillation counting becomes comparatively greater in course of time, and, hence, the importance of different sources of error varies in different analytical situations.

In the other experiments the mean values for the concentration of mercury in the organs were calculated from the data on the individual organs from each animal. On the other hand, the excretion data were obtained from the combined

sample. In experiment 4, however, excretion data were determined for each individual animal in the control group.

When comparing the mean values, obtained by either way, for the control and the therapy groups, it was not considered possible to apply either the analysis of variance or the *t*-test because the variance in the distribution of the concentration in the organs was not the same in a control group and in the corresponding treated groups. Instead, a confidence interval was calculated for the mean values of the control groups and, subsequently, it was tested whether the mean values of the treated groups fell within or outside this confidence interval.

In the groups where individual analytical values were available, standard deviation and confidence interval were calculated according the standard methods.

To judge by experiments 2, 3, and 4 the *coefficient of variation* is fairly constant for different concentrations in the organs. In order to obtain some idea of the confidence interval for the group mean value in experiment 1 the coefficients of variation from experiments 3 and 4 have been used. For phenyl mercury hydroxide and methoxyethyl mercury hydroxide there was no coefficient of variation exceeding 0.30 for concentrations in the organs of the control animals. For mercuric nitrate the highest coefficient of variation was 0.50 and for methyl mercury hydroxide 0.16.

These values have been used for estimating the coefficient of variation in experiment 1 to form the confidence interval for the mercury content of the organs taken together.

With regard to excretion data, individual analyses are available only in the control groups in experiment 4. In all the other cases the combined excretion of the group was analyzed. The coefficient of variation, for the amount of mercury excreted by the control animals in experiment 4, was in no case higher than 0.69. In the absence of more detailed data this figure was used to estimate the standard deviations and the confidence interval for the rest of the material.

From the estimated, standard deviations the confidence interval was calculated in the usual way according to the formula $z \cdot \sigma/\sqrt{N}$, with $z = \pm 1.96$, which gives a 95 per cent confidence interval, and $N = 5$, which is respectively the number of organs and the number of fecal or urinary samples that were taken together.

3.2.2. Results

The results of the investigations are given in Tables 5—11, where the concentrations in the organs and the excretion in the control groups and the treated groups are also compared. The criterion that treatment had produced an effect was, that the mean value for the treated group should fall outside the 95 per cent confidence interval for the mean value of the control group. If, in accordance with this, an effect was observed, this is indicated by + or — in the tables depending upon whether the experimental group showed an increase or a decrease, compared with the control group, with regard to concentration in the organs or to excretion. Absence of such an effect is indicated by 0. In several cases in experiment 1 concentration in the organs was so low that the standard deviations, calculated on the basis of double determinations, are of the same order of magnitude as the mean value. Such values have been excluded from the comparisons between treated

Table 5. *Experiment 1. Distribution of mercury in different organs. Standard deviation for double determinations and confidence interval as described in text. Effect of treatment given as described in text*

Mercury compound Dose in μg Hg/animal	Antidote		Concentration of mercury, ng/g				
			Blood	Liver	Kidney	Brain	Residue
Mercuric nitrate 10	Controls	Hg-concentration	5	37	1664	5	6
		Confidence interv. ±	—	17	749	—	—
	Penicill-amine	Hg-concentration	7	47	2320	4	5
		Effects		0	0		
	BAL	Hg-concentration	3	16	96	1	1
		Effects		—	—		
	EDTA	Hg-concentration	5	58	907	5	17
		Effects		+	—		
		Standard deviation for double determinations	2	5	35	6	5
Phenyl mercury hydroxide 10	Controls	Hg-concentration	6	81	1747	4	14
		Confidence interv. ±		21	454	1	4
	BAL	Hg-concentration	3	30	150	14	2
		Effects		—	—	(+)	(−)
	EDTA	Hg-concentration	9	89	1809	4	24
		Effects		0	0		
		Standard deviation double determinations	6	3	35	6	5
Methyl mercury hydroxide 20	Controls	Hg-concentration	427	165	594	39	75
		Confidence interv. ±	60	23	83	5	11
	Penicill-amine	Hg-concentration	327	145	728	36	75
		Effects	—	0	+	0	0
	BAL	Hg-concentration	389	149	385	54	84
		Effects	0	0	—	+	0
	EDTA	Hg-concentration	468	188	684	39	81
		Effects	0	0	+	0	0
		Standard deviation double determinations	32	5	34	6	5
Methoxy-ethyl mercury hydroxide 10	Controls	Hg-concentration	9	61	2462	9	7
		Confidence interv. ±		16	640		2
	BAL	Hg-concentration	7	24	120	9	16
		Effects		—	—		(+)
	EDTA	Hg-concentration	8	68	1683	8	18
		Effects		0	—		(+)
		Standard deviation double determinations	3	5	34	7	5

Table 6. *Experiment 2. Methoxyethyl mercury hydroxide injected intravenously in rats in a dose corresponding to 100 μg of Hg/animal. Treatment with different antidotes. Distribution of mercury in different organs. Confidence interval as described in text. Effect of treatment as described in text*

Antidote		Concentration of mercury, ng/g				
		Blood	Liver	Kidney	Brain	Residue
Controls	Hg-concentration	125	458	17,300	23	177
	Confidence interv. ±	27	208	3,200	3	70
Penicill-amine	Hg-concentration	85	634	5,310	18	173
	Effects	—	0	—	—	0
EDTA	Hg-concentration	102	413	7,350	25	130
	Effects	0	0	—	0	0

animals and control animals. If only one of the mean values in the comparison lies close to the limit of detection the + and — signs have been put in brackets.

A survey of the results is given in Table 11. Most of the antidotes applied have influenced both the distribution of mercury in the body and excretion in either direction. It should be pointed out that in these investigations the concentration of mercury was determined, but the analyses do not indicate the form in which the mercury was present. Thus, the stated changes in concentration refer to the content of mercury.

3.2.2.1. Mercuric Nitrate. Treatment with pernicillamine or ascorbic acid did not have an effect on the distribution of mercury among different organs. BAL and EDTA caused a decrease in the mercury content of the kidneys, whereas Rongalite C caused an increase. BAL, Rongalite C, Thiomalic acid, and PAS brought about a decrease in the mercury content of the liver. The blood concentration rose as a result of treatment with Thioctic acid and thioacetamide. Treatment with thioctic acid, Rongalite C, and thioacetamide caused an increased concentration in the testes.

Excretion was not influenced by treatment with penicillamine, EDTA, or ascorbic acid. Thioctic acid and thiomalic acid produced redistribution between urine and feces. Only BAL treatment gave rise to an increase in total excretion during the observation period of 3 days. The other substances brought about a decrease in the total excretion of mercury, with the exception of thiomalic acid, which caused only a redistribution.

3.2.2.2. Methyl Mercury Hydroxide. EDTA, ascorbic acid, and Rongalite C had no effect on the distribution of mercury between different organs. BAL, thioctic acid, and thiomalic acid produced a decreased mercury content in the kidneys, whereas penicillamine caused

Table 7. *Experiments 3 and 4. Distribution of mercury in different organs. Confidence intervals and effect as described in text*

Mercury compound Dose in µg Hg/ animal	Antidote		Concentration of mercury, ng/g					
			Blood	Liver	Kidney	Testes	Brain	Epididymis
Mercuric nitrate 100	Controls (exp. 4)	Hg-concentration	54	407	10,300	43	34	—
		Conf. interv. ±	20	126	5,300	13	15	—
	Thioctic acid	Hg-concentration	89	355	12,700	111	37	—
		Effects	+	0	0	+	0	
	Rongalite C	Hg-concentration	58	271	15,200	68	33	—
		Effects	0	—	+	+	0	
	Thiomalic acid	Hg-concentration	39	274	7,620	47	26	—
		Effects	0	—	0	0	0	
	Thioacetamide	Hg-concentration	119	382	5,830	87	41	—
		Effects	+	0	0	+	0	
	PAS	Hg-concentration	57	165	13,200	43	32	—
		Effects	0	—	0	0	0	
	Controls (exp. 3)	Hg-concentration	42	217	12,800	38	39	87
		Conf. interv. ±	20	126	5,300	13	15	13
	Ascorbic acid	Hg-concentration	37	222	11,800	36	36	87
		Effects	0	0	0	0	0	0
Phenyl mercury hydroxide 100	Controls (exp. 4)	Hg-concentration	40	333	14,900	32	17	—
		Conf. interv.	13	57	4,200	5	4	
	Thioctic acid	Hg-concentration	67	313	8,550	82	141	—
		Effects	+	0	—	+	+	
	Rongalite C	Hg-concentration	44	319	13,300	36	24	—
		Effects	0	0	0	0	+	
	Thiomalic acid	Hg-concentration	45	372	8,840	30	17	—
		Effects	0	0	—	0	0	
	Thioacetamide	Hg-concentration	38	233	12,200	31	19	—
		Effects	0	—	0	0	0	
	PAS	Hg-concentration	35	230	16,800	29	19	—
		Effects	0	—	0	0	0	
	Controls (exp. 3)	Hg-concentration	55	286	11,400	38	22	91
		Conf. interv.	11	51	3,700	5	4	14
	Ascorbic acid	Hg-concentration	40	277	7,900	35	18	87
		Effects	—	0	0	0	0	0
Methyl mercury hydroxide 100	Controls (exp. 4)	Hg-concentration	2160	523	1,730	136	128	—
		Conf. interv.	282	85	262	21	18	
	Thioctic acid	Hg-concentration	2560	424	1,390	137	236	—
		Effects	+	—	—	0	+	
	Rongalite C	Hg-concentration	2040	447	1,770	121	134	—
		Effects	0	0	0	0	0	

Table 7 (Continued)

Mercury compound. Dose in µg Hg/ animal	Antidote		Concentration of mercury, ng/g					
			Blood	Liver	Kidney	Testes	Brain	Epididymis
	Thiomalic acid	Hg-concentration	1380	407	1,150	86	95	—
		Effects	—	—	—	—	—	
	Thioacetamide	Hg-concentration	2460	352	2,250	156	147	—
		Effects	+	—	+	0	+	
	PAS	Hg-concentration	2140	380	1,890	137	143	—
		Effects	0	—	0	0	0	
	Controls (exp. 3)	Hg-concentration	2500	524	2,100	152	133	221
		Conf. interv.	282	85	262	21	18	27
	Ascorbic acid	Hg-concentration	2500	518	2,190	156	143	233
		Effects	0	0	0	0	0	0
Methoxyethyl mercury hydroxide 100	Controls (exp. 4)	Hg-concentration	68	297	17,100	37	18	—
		Conf. interv.	20	88	2,400	10	3	
	Thioctic acid	Hg-concentration	111	316	7,980	104	110	—
		Effects	+	0	—	+	+	
	Rongalite C	Hg-concentration	74	220	16,800	63	31	—
		Effects	0	0	0	+	+	
	Thiomalic acid	Hg-concentration	39	198	5,960	27	15	—
		Effects	—	—	—	0	0	
	Thioacetamide	Hg-concentration	61	180	7,660	44	22	—
		Effects	0	—	—	0	+	
	PAS	Hg-concentration	44	138	15,300	38	19	—
		Effects	0	—	0	0	0	
	Controls (exp. 3)	Hg-concentration	54	237	11,800	40	22	95
		Conf. interv.	20	88	2,400	10	3	33
	Ascorbic acid	Hg-concentration	33	217	12,500	39	18	72
		Effects	—	0	0	0	—	0
	Rongalite C	Hg-concentration	56	287	15,500	46	25	94
		Effects	0	0	+	0	+	0

an increase. BAL, thioctic acid, and thioacetamide caused an increase in the mercury content of the brain. Concentration in the liver was lowered on treatment with thioctic acid, thiomalic acid, thioacetamide, and PAS. Concentration in the blood was lowered following treatment with penicillamine, and thiomalic acid, but it increased on treatment with thioctic acid, and thioacetamide.

Total excretion was not affected by EDTA, ascorbic acid or PAS. Penicillamine, BAL, and thioctic acid caused redistribution, with increased urinary excretion and reduced fecal excretion, whereas total

Table 8. *Experiment 1. Excretion of mercury in urine and feces. Confidence limits and effect of antidotes given as described in text*

Mercury compound	Antidote	Accumulated excretion in μg per animal								
		Day 1			Day 1 + 2			Day 1 + 2 + 3		
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
Mercuric nitrate	Controls									
	Excretion	0.190	0.472	0.662	0.340	1.060	1.400	0.420	1.490	1.910
	Conf. interv.	0.114	0.284	0.397	0.204	0.640	0.840	0.252	0.890	1.150
	Penicillamine									
	Excretion	0.184	0.358	0.542	0.452	0.996	1.450	0.572	1.260	1.830
	Effects	0	0	0	0	0	0	0	0	0
	BAL									
	Excretion	0.730	0.680	1.410	1.290	1.960	3.250	1.350	2.340	3.690
	Effects	+	0	+	+	+	+	+	0	+
	EDTA									
	Excretion	0.306	0.566	0.872	0.518	1.490	2.010	0.610	1.810	2.420
	Effects	+	0	0	0	0	0	0	0	0
Phenyl mercury hydroxide	Controls									
	Excretion	0.178	0.758	0.936	*					
	Conf. interv.	0.107	0.455	0.562						
	BAL									
	Excretion	1.580	2.150	3.730						
	Effects	+	+	+						
	EDTA									
	Excretion	0.208	0.854	1.060						
	Effects	0	0	0						
Methyl mercury hydroxide	Controls									
	Excretion	0.190	0.394	0.584	0.242	0.888	1.130	0.290	1.410	1.700
	Conf. interv.	0.114	0.236	0.350	0.145	0.532	0.680	0.174	0.850	1.020
	Penicillamine									
	Excretion	0.712	0.348	1.060	1.000	0.968	1.970	1.110	1.330	2.440
	Effects	+	0	+	+	0	+	+	0	0
	BAL									
	Excretion	0.380	0.286	0.666	0.552	0.786	1.340	0.644	1.220	1.870
	Effects	+	0	0	+	0	0	+	0	0
	EDTA									
	Excretion	0.124	0.324	0.448	0.170	0.858	1.030	0.224	1.330	1.560
	Effects	0	0	0	0	0	0	0	0	0
Methoxy-ethyl mercury hydroxide	Controls									
	Excretion	0.212	1.610	1.820	0.406	2.240	2.650	0.484	2.610	3.100
	Conf. interv.	0.127	0.960	1.090	0.244	1.350	1.590	0.290	1.570	1.860
	BAL									
	Excretion	1.100	1.600	2.700	1.580	1.860	3.440	1.650	2.270	3.920
	Effects	+	0	0	+	0	0	+	0	0
	EDTA									
	Excretion	0.458	2.540	3.000	0.876	3.920	4.800	1.120	4.600	5.720
	Effects	+	0	+	+	+	+	+	+	+

* The samples were lost.

excretion remained unchanged. Rongalite C produced a redistribution, with decreased urinary excretion and increased fecal excretion, and unchanged total excretion during the observation period. Thiomalic acid and thioacetamide caused a very substantial increase in excretion via the urine, which resulted in a significant increase in the total excretion. This increase is most noticeable during the first 24 hours.

3.2.2.3. Phenyl Mercury Hydroxide. The effect of penicillamine on the phenyl mercury compound was not investigated. EDTA did not influence the distribution between the organs. BAL, thioctic acid, and thiomalic acid caused decreased concentration in the kidneys, whereas BAL, thioacetamide, and PAS caused a decreased concentration in the liver. BAL, thioctic acid, and Rongalite C produced increased mercury concentration in the brain, and thioctic acid produced an increase in both brain and testes. Ascorbic acid occasioned a decrease in the blood, and thioctic acid an increase.

EDTA and Rongalite C had no effect on excretion. BAL, thioctic acid, thioacetamide, and PAS brought about increased excretion via both feces and urine. Thiomalic acid caused an increase in the urinary excretion of mercury; this was too small, however, to influence significantly total excretion.

3.2.2.4. Methoxyethyl Mercury Hydroxide. None of the antidotes tested had any influence on the distribution between the organs. Penicillamine, BAL, EDTA, thioctic acid, thiomalic acid, and thioacetamide all caused a decreased mercury content in the kidneys, whereas Rongalite C possibly caused an increase. Penicillamine and ascorbic acid seemed to produce an decrease in the mercury content in the brain, whereas thioctic acid, Rongalite C, and thioacetamide produced an increase. The concentration in the liver was lowered as a result of treatment with BAL, thiomalic acid, thioacetamide, and PAS, whereas the other antidotes had no effect on the liver concentration. The mercury content in the blood was decreased by pencillamine, ascorbic acid, and thiomalic acid, whereas it was increased through treatment with thioctic acid. Thioctic acid and Rongalite C seemed to cause an increase in the mercury content in the testes.

Penicillamine produced an increase in excretion during the first 24 hours, which was mainly due to a strong urinary increase in the excretion of mercury, whereas fecal excretion diminished. During the observation period of 3 days total excretion, however, was not affected. EDTA caused an increase in the total excretion, principally owing to increased urinary excretion. Ascorbic acid may possibly have produced a decrease in urinary excretion. In this experiment the fecal samples were lost. BAL caused increased urinary excretion of mercury, but total

Table 9. *Experiments 2 and 3. Excretion of mercury in urine and feces. Confidence limits and antidote effects registered as described in text. Accumulated excretion in μg per animal*

		Day 1			Day 1 + 2			Day 1 + 2 + 3		
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
Methoxyethyl-mercury hydroxide (Exper. 2)	Controls									
	Excretion	4.520	3.520	8.040	8.120	16.100	24.200	9.920	22.000	31.900
	Conf. interv.	2.710	2.100	4.800	4.800	9.600	14.500	5.950	13.200	19.200
	Penicillamine									
	Excretion	16.500	1.300	17.800	20.600	13.200	33.800	23.000	19.800	42.800
	Effects	+	—	+	+	0	0	+	0	0
	EDTA									
	Excretion	12.100	4.080	16.200	23.700	18.900	42.600	27.000	28.600	55.600
	Effects	+	0	+	+	0	+	+	0	+
Methoxyethyl mercury hydroxide (Exper. 3)	Controls									
	Excretion	9.680	14.200	23.900	18.200	22.500	40.700	22.800	27.800	50.600
	Conf. interv.	5.810	8.500	14.300	10.900	13.500	24.400	13.700	16.700	30.400
	Ascorbic acid									
	Excretion	3.300	—*	—	10.700	—*	—	13.900	—*	—
	Effects	—			0			0		
	Rongalite C									
	Excretion	3.120	5.900	9.020	6.620	14.300	20.900	7.780	18.500	26.400
	Effects	—	0	—	—	0	0	—	0	0
Mercuric nitrate (Exper. 3)	Controls									
	Excretion	6.100	5.360	11.460	11.800	12.400	24.200	14.700	18.100	32.800
	Conf. interv.	3.660	3.220	6.900	7.100	7.400	14.500	8.800	10.800	19.700
	Ascorbic acid									
	Excretion	6.590	7.190	13.780	12.800	16.500	29.300	15.400	20.800	36.200
	Effects	0	0	0	0	0	0	0	0	0

Phenyl mercury hydroxide (Exper. 3)	Controls										
	Excretion	4.260	7.360	11.620	8.800	16.800	25.680	11.400	21.900	33.300	
	Conf. interv.	2.560	4.410	7.000	5.330	10.100	15.400	6.800	13.100	20.000	
	Ascorbic acid										
	Excretion	8.820	11.000	19.820	16.700	22.800	39.500	20.800	28.600	49.400	
	Effects	+	0	+	+	0	0	+	0	0	
Methyl mercury hydroxide (Exper. 3)	Controls										
	Excretion	0.270	2.660	2.930	0.531	6.880	7.411	0.810	10.500	11.310	
	Conf. interv.	0.163	1.590	1.760	0.319	4.130	4.450	0.486	6.300	6.800	
	Ascorbic acid										
	Excretion	0.258	3.180	3.440	0.516	8.580	9.096	0.790	12.100	22.890	
	Effects	0	0	0	0	0	0	0	0	0	

* Samples were lost.

excretion was not affected. With thioctic acid, Rongalite C, thioacetamide, and PAS there was an increase in excretion via the feces, whereas with thiomalic acid increased excretion was via the urine.

3.3. Summary and Discussion

In the present investigation our aim has been to study the antidotal effects which may possibly be of significance for practical therapy. Consequently, we have been interested only in manifest effects on survival, and have been content to investigate small groups of animals, and have merely reported total mortality during certain observation periods. It is, of course, conceivable that, in this way, some minor antidotal effects may not have been recorded, but we considered that such minor effects could hardly prove of practical therapeutic importance in actual cases of poisoning, and therefore we have consciously accepted this possibility of oversight. Nor have we, in general, attached any importance to the fact that death occurred either sooner or later in some treated groups than in the control group, a fact which, in a larger material, might indicate an effect in a positive or negative direction of the antidote in question.

The pattern of effect of different antidotes on distribution of mercury in various organs and on excretion of different mercury compounds is very complex. Here we shall merely try to indicate some of the most noteworthy features. Since in this investigation our purpose was to deal

Table 10. *Experiment 4. Excretion of mercury in urine and feces. Confidence limits and effect of antidotes given as described in text*

Mercury compound	Antidote	Accumulated excretion in μg per animal								
		Day 1			Day 1 + 2			Day 1 + 2 + 3		
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
Mercuric nitrate	Controls									
	Hg-excretion	10.300	10.900	21.200	18.400	23.400	41.800	25.100	30.700	55.900
	Conf. lim. ±	5.800	3.800	9.300	6.000	7.700	12.300	7.400	12.000	19.000
	Thioctic acid									
	Hg-excretion	1.700	9.200	10.900	2.600	14.000	16.600	5.200	22.100	27.300
	Effects	—	0	—	—	—	—	—	0	—
	Rongalite C									
	Hg-excretion	8.400	3.400	11.800	9.700	7.900	17.600	13.000	14.400	27.400
	Effects	0	—	—	—	—	—	—	—	—
	Thiomalic acid									
	Hg-excretion	35.200	3.400	38.600	36.600	7.600	44.200	41.800	16.100	57.900
	Effects	+	—	+	+	—	0	+	—	0
	Thioacetamide									
	Hg-excretion	7.700	4.900	12.600	9.700	9.800	19.500	13.000	14.200	27.200
	Effects	0	—	0	—	—	—	—	—	—
	PAS									
	Hg-excretion	5.400	4.100	9.500	8.700	10.900	19.600	11.300	16.600	27.800
	Effects	0	—	—	—	—	—	—	—	—
Phenyl mercury hydroxide	Controls									
	Hg-excretion	1.570	15.900	17.500	2.710	37.400	40.100	3.590	44.400	47.990
	Conf. lim. ±	0.580	7.700	6.600	0.820	8.100	7.700	1.050	7.900	7.700
	Thioctic acid									
	Hg-excretion	2.200	27.600	29.800	4.000	44.600	48.600	6.000	57.000	63.000
	Effects	0	+	+	+	0	+	+	+	+

	Rongalite C									
	Hg-excretion	2.400	21.200	23.900	3.600	39.400	43.000	4.300	46.400	50.700
	Effects	+	0	0	+	0	0	0	0	0
	Thiomalic acid									
	Hg-excretion	21.200	14.200	35.400	26.600	37.200	63.800	29.800	44.200	74.000
	Effects	+	0	+	+	0	+	+	0	+
	Thioacetamide									
	Hg-excretion	3.500	24.600	28.100	7.200	48.000	55.200	12.200	56.200	68.400
	Effects	+	+	+	+	+	+	+	+	+
	PAS									
	Hg-excretion	2.700	24.600	27.300	5.200	54.800	60.000	6.700	62.800	69.600
	Effects	+	+	+	+	+	+	+	+	+
Methyl mercury hydroxide	Controls									
	Hg-excretion	0.438	3.120	3.558	0.862	5.660	6.522	1.190	8.140	9.340
	Conf. lim. ±	0.302	2.690	2.500	0.196	3.830	3.790	0.220	4.210	4.110
	Thioctic acid									
	Hg-excretion	1.150	2.000	3.150	2.100	4.940	7.040	2.680	8.160	10.840
	Effects	+	0	0	+	0	0	+	0	0
	Rongalite C									
	Hg-excretion	0.324	2.620	2.944	0,582	5.220	5.802	0.752	8.560	9.312
	Effects	0	0	0	−	0	0	−	0	0
	Thiomalic acid									
	Hg-excretion	7.300	2.240	9.540	12.800	5.240	18.040	16.800	7.540	24.340
	Effects	+	0	+	+	0	+	+	0	+
	Thioacetamide									
	Hg-excretion	5.380	2.740	8.120	5.840	5.500	11.300	6.340	7.920	14.260
	Effects	+	0	+	+	0	+	+	0	+
	PAS									
	Hg-excretion	0.438	2.680	3.118	0.756	5.960	6.716	1.100	9.660	10.760
	Effects	0	0	0	0	0	0	0	0	0

Table 10 (Continued)

Mercury compound	Antidote	Accumulated excretion in μg per animal								
		Day 1			Day 1+2			Day 1+2+3		
		Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
Methoxyethyl mercury hydroxide	Controls									
	Hg-excretion	5.180	7.300	12.450	9.500	18.200	27.700	11.600	26.500	38.100
	Conf. limits ±	6.600	5.800	6.400	8.100	5.700	10.000	8.200	17.400	15.100
	Thioctic acid									
	Hg-excretion	3.400	14.300	17.700	13.000	45.000	58.300	14.400	51.800	66.200
	Effects	0	+	0	0	+	+	0	+	+
	Rongalite C									
8	Hg-excretion	3.900	11.200	15.100	11.400	42.200	53.600	13.100	47.400	60.500
	Effects	0	0	0	0	+	+	0	+	+
	Thiomalic acid									
	Hg-excretion	30.400	6.600	37.000	40.200	22.600	62.800	42.600	26.500	69.100
	Effects	+	0	+	+	0	+	+	0	+
	Thioacetamide									
	Hg-excretion	4.900	13.000	17.900	15.100	30.600	45.700	19.800	36.000	55.800
	Effects	0	0	0	0	+	+	0	0	+
	PAS									
	Hg-excretion	4.700	12.500	17.200	10.000	36.700	46.700	12.400	43.200	55.600
	Effects	0	0	0	0	+	+	0	0	+

with a practical problem, namely, the possibilities of effective therapy in cases of poisoning by mercury compounds of different types, it is naturally, also of importance to study the extent to which therapeutic effects are correlated with the effects on excretion and/or redistribution in connection with treatment with different antidotes.

3.3.1. BAL

BAL had a distinct therapeutic effect on poisoning by mercuric nitrate and phenyl mercury hydroxide, both when treatment was applied immediately and when it was applied 4 hours after injection of the mercury compound. On the other hand, BAL treatment had no effect at all on poisoning by methyl mercury hydroxide; and on poisoning by methoxyethyl mercury hydroxide it had a directly negative effect, all the animals died in direct connection with the second injection of BAL. With regard to methyl mercury hydroxide the results confirm the experience of GLÖMME and GUSTAVSON (1959).

For all the types of mercury compounds studied, BAL treatment seemed to cause an increase in urinary excretion of mercury and a decrease in the mercury content in the kidneys. For mercuric nitrate and phenyl mercury hydroxide total excretion was increased, whereas this was not affected in the case of methyl and methoxyethyl mercury hydroxide. With regard to methyl mercury hydroxide BAL treatment did not produce any change in the mercury content of the liver, whereas for the other mercury compounds studied there was a decrease.

BAL treatment, after administration of methyl mercury hydroxide caused an increase in the deposition of mercury in the brain, which had already been demonstrated earlier by ULFVARSON (1962). Thus, with BAL treatment there is quite a regular pattern of effects, where the results with methyl mercury hydroxide diverge from those for the other mercury compounds.

We can show that BAL treatment has a distinct life-saving effect in acute poisoning by mercuric nitrate and by phenyl mercury hydroxide, whereas it has no such effect on poisoning by methyl mercury hydroxide, and a definitely negative effect on poisoning by the methoxyethyl mercury compound. In all the cases there was increased urinary excretion of mercury as a result of treatment. The increase in excretion can, of course, have been the cause of the therapeutic results; and, consequently, in those cases where no therapeutic effect occurred, the increase in excretion must have been too slight to bring about the desired action. What seems to refute this view is, that in cases of poisoning by small doses there is also no life-saving effect. It is likewise conceivable that a redistribution of mercury, due to treatment, may be the decisive factor.

Table 11. *Survey of the effects of different antidotes upon the distribution and excretion of mercury after injection of different mercury compounds. + denotes an increase, — a decrease and 0 no significant changes in relation to untreated control animals, that have received only the mercury compound. B = blood, L = liver, K = kidney, T = testes, Br = brain, E = epididymis, R = residue, U = urine, F = feces*

Antidote	Mercury compound	Effects on mercury concentration in different organs							Effects on excretion in three days		
		B	L	K	T	Br	E	R	U	F	U+F
Penicillamine	Mercuric nitrate		0	0					0	0	0
	Methoxyethyl mercury hydroxide	—	0	—		—		0	+	0	0
	Methyl mercury hydroxide	—	0	+		0		0	+	0	0
BAL	Mercuric nitrate		—	—					+	0	+
	Phenyl mercury hydroxide		—	—		(+)		(−)	+	+	+
	Methoxyethyl mercury hydroxide		—	—				(+)	+	0	0
	Methyl mercury hydroxide	0	0	—		+		0	+	0	0
EDTA	Mercuric nitrate		+	—				(+)	0	0	0
	Phenyl mercury hydroxide		0	0					0	0	0
	Methoxyethyl mercury hydroxide I		0	—				(+)	+	+	+
	II	0	0	—		0		0	+	0	+
	Methyl mercury hydroxide	0	0	0		0		0	0	0	0
Ascorbic acid	Mercuric nitrate	0	0	0	0	0	0		0	0	0
	Phenyl mercury hydroxide	—	0	0	0	0	0		+	0	0
	Methoxyethyl mercury hydroxide	—	0	0	0	—	0		0		
	Methyl mercury hydroxide	0	0	0	0	0	0		0	0	0
Thioctic acid	Mercuric nitrate	+	0	0	+	0			—	0	—
	Phenyl mercury hydroxide	+	0	—	+	+			+	+	+
	Methoxyethyl mercury hydroxide	+	0	—	+	+			0	+	+
	Methyl mercury hydroxide	+	—	—	0	+			+	0	0
Rongalite C	Mercuric nitrate	0	—	+	+	0			—	—	—
	Phenyl mercury hydroxide	0	0	0	0	+			0	0	0

	Methoxyethyl mercury hydroxide I	0	0	0	+	+	0	+	+
	II	0	0	+	0	+	—	0	0
	Methyl mercury hydroxide	0	0	0	0	0	—	0	0
Thiomalic acid	Mercuric nitrate	0	—	0	0	0	+	—	0
	Phenyl mercury hydroxide	0	0	—	0	0	+	0	+
	Methoxyethyl mercury hydroxide	—	—	—	0	0	+	0	+
	Methyl mercury hydroxide	—	—	—	—	—	+	0	+
Thioacetamide	Mercuric nitrate	+	0	0	+	0	—	—	—
	Phenyl mercury hydroxide	0	—	0	0	0	+	+	+
	Methoxyethyl mercury hydroxide	0	—	—	0	+	0	0	+
	Methyl mercury hydroxide	+	—	+	0	+	+	0	+
PAS	Mercuric nitrate	0	—	0	0	0	—	—	—
	Phenyl mercury hydroxide	0	—	0	0	0	+	+	+
	Methoxyethyl mercury hydroxide	0	—	0	0	0	0	0	+
	Methyl mercury hydroxide	0	—	0	0	0	0	0	0

A number of other observations, to which we shall refer later, indicate that this factor is of great importance.

It has been asserted in some publications that BAL treatment has a therapeutic effect on poisoning by alkyl mercury compounds (AHLBORG and AHLMARK, 1949; ENGLESON and HERNER, 1952; JALILI and ABBASI, 1961). In a case of alkyl mercury poisoning, HÖÖK, LUNDGREN and SWENSSON found that BAL treatment had no therapeutic effect. In another case, with slight sequels after poisoning they found a small increase in urinary mercury excretion on BAL treatment and at the same time some clinical improvement. This was regarded as possibly being due to the mobilization of a small amount of mercury, which had been liberated, in the organism, from the methyl bond. On the basis of the data given in the few publications available, it was not possible to assess the therapeutic value of BAL treatment in cases of alkyl mercury poisoning. According to our results, data on the urinary excretion of mercury are no indication of a therapeutic effect. When determining one's attitude to the question concerning the application of BAL treatment in cases of acute poisoning by alkyl mercury compounds, it is also important to take into consideration that the treatment can lead to an increased uptake of mercury in the brain; and that in this

type of poisoning the central nervous system is the organ from which the symptoms emanate. In view of the fact that the therapeutic effect seems to be non-existent or, at any rate, very slight, BAL treatment should not be used in cases of acute poisoning by alkyl mercury compounds, because of the risk of an increased flow of mercury into the nervous system.

3.3.2. EDTA

In a number of cases the EDTA-treatment resulted in a more rapid lethal course than that in untreated animals. This confirms the results previously reported by, for example, TURRIAN. GRANDJEAN, BÄTTIG, and TURRIAN (1956), and GLÖMME and GUSTAVSON (1959).

It should be recognized that treatment with Ca-Na_2-EDTA has no life-saving effect in respect of poisoning by any of the mercury compounds studied here, and that its application is not advisable, since it is possible that it may exacerbate the situation. At any rate, an ineffective EDTA treatment delays the introduction of some other therapy that may be more effective.

EDTA treatment after the administration of methoxyethyl mercury hydroxide caused an increase in the excretion of mercury, a result which was repeated in two different experiments. In both experiments there was also a slight decrease in the concentration of mercury in the kidneys. Otherwise, EDTA treatment did not produce any change in the excretion of mercury; and only in the case of mercuric nitrate did it have any influence on the distribution of mercury.

3.3.3. D-*Penicillamine*

Penicillamine has a life-saving effect in cases of acute poisoning by mercuric nitrate and methoxyethyl mercury hydroxide. In the former case the antidote was effective both when the treatment was applied immediately and when it was first given 4 hours after administration of the mercury compound. In the latter case the antidote was effective only when treatment was applied immediately.

The experiments show that it is important that the dose of the antidote is sufficiently large, otherwise the treatment is completely ineffective.

With penicillamine treatment no effect was obtained either on the excretion of mercury or on its distribution in the organs in the case of mercuric nitrate. That it has a definite life-saving effect despite this, shows that the therapeutic effect is not absolutely dependent upon the excretion of the poison or even on its redistribution between the organs. The effect may possibly be explained by redistribution in the organs/cells or, perhaps, by the conversion of the poison into some other form.

On the other hand, treatment caused an increase in the urinary excretion of mercury and a lowering of the concentration in the blood when the methyl or methoxyethyl mercury compound was administered. In the former case there was an increase, and in the latter a decrease, in the mercury content in the kidneys. Thus, with regard to the methyl mercury compound, increase in excretion did not result in any increase in the survival rate.

3.3.4. Ascorbic acid

In general, ascorbic acid had no effect on the survival rate or on distribution in the organs and excretion. In the individual instances where an effect on distribution in the organs or on excretion seems to have occurred, this may very well have been due to random variations within the confidence limits we chose.

3.3.5. Thioctic acid

If treatment was given immediately thioctic acid had a life-saving effect in acute poisoning by mercuric nitrate or phenyl mercury hydroxide, but had no effect on the other two compounds. In no case had the antidote any effect if treatment was applied after a latency period of 4 hours.

When mercuric nitrate was used, thioctic acid caused a decrease in the excretion of Hg and an increase in the mercury content of the blood and testes, but no certain variations in the other organs. With regard to the other mercury compounds, treatment produced a more or less manifest increase in excretion and a simultaneous decrease in the concentration of mercury in the kidneys. The treatment also resulted in an increased mercury concentration in the blood and in the brain. It is worthy of note that treatment with thioctic acid caused an increased uptake in the brain on administration of all the three organic mercury compounds studied. This should, of course, be taken into account when considering therapeutics.

3.3.6. Rongalite C

If treatment with Rongalite C is applied immediately this results in a higher survival rate in cases of poisoning by mercuric nitrate, phenyl and methoxyethyl mercury hydroxide, but not by methyl mercury hydroxide. There is a clear decrease in mercury excretion in poisoning with mercuric nitrate, and an increase in the concentration of mercury in the kidneys, but a decrease in the liver. In regard to the phenyl mercury compound there was no change in the excretion of mercury,

and as regards distribution in the organs there was only an increase in the mercury content of the brain in Rongalite C treatment. For the methoxyethyl compound the changes are slight, which causes a certain difference between the two experiments. Throughout the mercury content of the brain was increased. In the case of methyl compound the treatment caused a decrease in excretion and distribution in the organs remained unchanged.

3.3.7. Thiomalic acid

Treatment with thiomalic acid caused throughout an increase in urinary excretion of mercury. In the case of mercuric nitrate there was at the same time a decrease in fecal excretion resulting in unchanged total excretion. With regard to the other mercury compounds treatment brought about an increase in total excretion. For methyl mercury hydroxide this increased excretion led to a general reduction in the mercury content of all the organs investigated. Despite this the treatment had no life-saving effect. The same tendency could be observed in regard to the methoxyethyl mercury compound. For the other two compounds a certain reduction in the mercury content of the organs was obtained, never any increase.

In no case did thiomalic acid give rise to a higher survival rate.

3.3.8. Thioacetamide

In no case did the treatment have any effect on the survival rate in acute poisoning by the mercury compounds studied.

In the case of mercuric nitrate, thioacetamide caused a distinct decrease in both urinary and fecal excretion of mercury and at the same time an increase in the mercury content in the kidneys and blood. With phenyl mercury hydroxide an entirely contrary effect was obtained: increased mercury excretion in both urine and feces and a decrease in the mercury content of the liver. With methyl and methoxyethyl mercury hydroxide, thioacetamide treatment produced a certain increase in excretion. In these cases redistribution was less clear. For methyl mercury hydroxide there was a reduction in the mercury content in the liver and an increase in that of the blood and kidneys. Both these compounds accumulate to a greater extent in the brain on treatment with thioacetamide.

3.3.9. PAS

PAS seemed to cause a higher survival rate for acute poisoning by phenyl mercury hydroxide when treatment was applied 4 hours after

injection of the inorganic mercury compound. Since this was the only case where a therapeutic effect was observed, and it is strange that the antidote should have been more effective when treatment was applied later than it was when treatment was applied immediately, it was probably due to random variation. The question can be settled only if further investigations are made with a larger material. We think that, on the basis of the investigations made hitherto, PAS cannot be regarded as producing any therapeutic effect in acute poisoning by the mercury compounds studied here. We did not continue the investigations because we did not consider there was any reason for assuming that PAS might be more effective than BAL for this special type of poisoning and, consequently, there was nothing essential to be gained from a practical point of view.

PAS treatment caused a distinct decrease in both the urinary and fecal excretion of mercury in the case of mercuric nitrate. Quite the opposite result was obtained with phenyl mercury hydroxide: an increase in excretion in both urine and feces. Moreover, in regard to methoxyethyl mercury hydroxide an increased total excretion was observed.

In respect of mercury distribution in the different organs, a decrease in the liver and no change in the other organs was noted throughout. This means, of course, that the increases, which must in reality occur in some of the organs where the mercury which overflows from the liver is dealt with to the extent that it is not excreted, is too small to find expression in this investigation.

3.3.10. Summary

In our investigations, the treatment, of acute poisoning by mercury compounds of different types, with BAL, D-penicillamine, Rongalite C, and thioctic acid, showed an increase in the survival rate. The effect of PAS in one case may have been due to a chance variation, and requires to be checked before it can be accepted as definitely established. The other antidotes studied had no life-saving effect.

The therapeutic effect of an antidote varied, and depended upon the type of mercury compound that had caused the poisoning. There were also great differences between the various antidotes used with regard to their influence on the excretion of mercury and its distribution between the different organs. Furthermore, the effect of one and the same antidote differs according to the types of mercury compounds to which they are applied. As a general assessment it might probably be stated that, on the whole, ascorbic acid, did not have any essential effect. When BAL and thiomalic acid were used, all the mercury compounds studied showed an increase in excretion, which corresponded

to certain rather similar decreases in the content of the organs. For the other antidotes the results were more varying. It is important to point out that treatment with BAL, thioctic acid, Rongalite C, and thioacetamide caused, in several cases, an increase in the mercury content of the brain, even in cases where there was increased mercury excretion as a result of treatment. In view of the sensitivity of the central nervous system to mercury, this is a very important observation in regard to practical therapy.

With certain antidotes, for example, thioctic acid, thioacetamide, and PAS, a diametrically opposed effect on excretion was observed in the case of mercuric nitrate and phenyl mercury hydroxide. This may probably be interpreted as indicating that these compounds behave in an entirely different way in the organism, and that the phenyl mercury compound, at any rate during the short time the experiment lasted, remained mainly intact.

A persistent characteristic throughout was that the methyl mercury compound was less affected by the administration of the antidotes than were the rest of the mercury compounds studied. In this case the strongest effect was produced by thiomalic acid.

The effect of PAS, where there was throughout a reduction in the mercury content in the liver, without any essential changes in the other organs, is a peculiar feature that cannot be assessed without more detailed investigations.

It is evident that, by administering different substances which, according to the information given in the literature, are antidotes against poisoning by mercury compounds, extensive changes in distribution and in the excretion of mercury can be accomplished. It is also abundantly clear that the effect of various antidotes is entirely different when they are used in cases of poisoning by mercury compounds of different types.

It is apparent that an increase in the survival rate need not be tied to an increase in the excretion of mercury or even to an increase or decrease in the mercury content in a certain organ. When a therapeutic effect occurs, it is probable that the mercury ion or mercury complex is detached from its cellular bond and, instead becomes bound to the antidote, as a basis for the therapeutic effect. This new compound, however, does not necessarily have to be conveyed away. Conversely, it is conceivable that some mercury is removed from an organ, but at the same time there is a redisposition in the cells, which may cause a more injurious condition in the organ than when the content was greater, and thereby increase mortality despite the decrease in the mercury content in the organs, especially when it is in a critical organ.

4. Conclusion

We have studied in animal experiments the influence of a series of substances which, according to the literature, have an antidotal effect on cases of "mercury poisoning". We have tested their antidotal effect in acute poisoning by mercury compounds of different types, and also their effect on the distribution of mercury in different organs and on its excretion.

1. The therapeutic effect differs depending on the mercury compound causing the poisoning.

In acute poisoning by inorganic mercury salts we found that BAL, D-penicillamine, thioctic acid, and Rongalite C had a therapeutic effect. With the two last-mentioned substances therapy must be applied immediately.

In acute poisoning by the methyl mercury compound no antidote had any life-saving effect.

In poisoning with the phenyl mercury compound, BAL had a marked life-saving effect; and so had Rongalite C and thioctic acid when therapy was given at once.

In acute poisoning by the methoxyethyl mercury compound, Rongalite C had some effect when given immediately. Penicillamine may have some effect. In this case BAL had a strongly negative effect and all animals died of convulsions in direct connection with the second injection of BAL. The mechanism of the reaction is not known.

2. All the antidotes tested, with the possible exception of ascorbic acid, had some influence on the excretion and distribution of mercury in different organs. This influence may be different for the same antidote when applied to different mercury compounds.

3. There is no definite connection between the life-saving effect of an antidote and its effect on distribution or excretion of mercury. An increase in excretion of mercury is not a precondition for a life-saving effect.

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