MERCURIAL DIURETICS

THE ADDITION OF MAGNESIUM SULPHATE TO PREVENT THE TOXIC EFFECTS OF THEIR INTRAVENOUS ADMINISTRATION

BY

IGNACY PINES, ANTONIO SANABRIA, AND R.T. HERNANDEZ ARRIENS

From the Department of Cardiology, Central University of Venezuela

Received October 30, 1944

The importance of mercurial diuretics in the treatment of heart failure has been obvious ever since the discovery of these useful drugs. Subsequent studies have explained to some extent the mechanism of their action. The relief afforded to the heart by the administration of mercurial diuretics in cardiac failure depends on the elimination of oedema, on the decrease of the volume of circulating blood, and sometimes on the fall of the arterial blood pressure. The interaction of these factors throws much less burden upon the exhausted heart. The disappearance of oedema is itself of great importance. This is accompanied, as has been shown by Blalock et al., by the decrease of the volume of blood flow needed by the tissues for their metabolic requirements, and a reduction of the mechanical resistance of the tissues to the flow of blood. The fall of blood pressure noted many times by various observers after the improvement of the circulation, which can perhaps be attributed to the diminution of local venous pressure in the kidney (Corrigan and Pines), acts also in the same direction.

To these must sometimes be added an increase in the functional capacity of the heart muscle because of a decrease in the heart oedema itself, as well as the complicated effects of the relief of congestion of other important organs. So, for instance, the diuresis after mercurial diuretics has a very favourable influence upon cardiac dyspnœa and on the congestion of the lungs. Also the abdominal circulation is much improved because there is less engorgement of the liver. Finally, the disappearance of the discomfort to which the patient with heart failure is exposed, the recession of insomnia and of the cough, the improved absorption of certain nutritional factors and in particular of vitamins, the decrease of basal metabolism, all these and other factors make the improvement due to diuresis induced by mercurial diuretics even more striking.

It is not surprising, therefore, that mercurial diuretics are highly rated amongst other drugs used in heart failure. According to Thomson, Marvin, and others their diuretic effects are often as great with digitalis as without it. Fishberg points out that they not only supplement the digitalis, but instances are not rare in which mercurials are decidedly more efficacious than digitalis itself. Withering's discovery is considered generally to be the opening of the first chapter in the efficient treatment of heart failure. There cannot be the slightest doubt, then, that the introduction of mercurial diuretics by Saxl and Heilig has marked the beginning of the second period.

The diuretic properties of mercurials were known, of course, even before the papers of Viennese authors appeared. According to Goodman and Gilman, calomel was used by Paracelsus for this purpose in the sixteenth century. Later on, Jendrassik, in 1886, confirmed the beneficial action of this drug upon patients suffering from cardiac dropsy. Fourneau and
Mellville 9 quote the important investigations of Blumenthal and Oppenheim 10 in which several organic and inorganic mercury compounds were studied and demonstrated, perhaps with the exception of mercury chloride, to possess various grades of diuretic activities. Nevertheless, the true interest of clinicians was aroused only by the introduction of mercury salicylate by Saxl and Heilig 6 and only since then the mercurial diuretics have been commonly used in the clinic for the treatment of cardiac dropsy and other diseases accompanied by the accumulation of important amounts of fluid in the tissues. This was due perhaps to the fact that, as was proved by the last mentioned authors, mercury salicylate or merbafen and even the less toxic salyrgan or mersalyl, produce much more pronounced diuresis than other mercury compounds, as for instance, mercury chloride or mercury succinate.

Since the beginning of the era of the mercurial diuretics, however, it has been known that they are not without certain toxic influence. Saxl 11 was clearly opposed to the administration of these diuretics in cases of severe anaemia, cachexia, fever, or diarrhea, and advised great prudence in dealing with patients whose blood pressure was above 200 mm. The most pronounced toxic effects were, of course, registered at the sites of the excretion of mercury from the body, i.e. the kidney and colon. The essence of the diuretic action itself consists chiefly, as was demonstrated, of the irritation of the renal tubules by the mercurial ion and "represents a very early stage of the toxic action of mercury on the kidney " (Goodman and Gilman 7). The administration of mercurial diuretics is accompanied sometimes, therefore, by the appearance in the urine of hyaline and granular casts, albumin, leucocytes, and erythrocytes, and by more or less marked degeneration of the epithelium of the tubules. The effects on the digestive apparatus, on the other hand, are also those of typical mercury poisoning and appear in the form of stomatitis, salivation, and haemorrhagic colitis. These changes, if present before the administration of mercurial diuretics, were automatic contra-indications against their use. Nevertheless, with greater experience acquired in dealing with these drugs, the initial precautions taken in their administration were to some extent relaxed. Amongst kidney diseases, cases of nephrosis or amyloidosis react sometimes beautifully to mercurial diuretics and no physician will hesitate to use them to free the patient from the great discomfort and danger of anasarca. The signs which were originally considered as strong contra-indications, as for instance, albuminuria, heightened blood pressure, presence of increased amount of casts and red blood cells in the urine, increase of non-protein nitrogen in blood, are known to accompany sometimes the stasis kidney and do not exclude a priori the use of these valuable drugs. The only important contra-indications that remain from the renal point of view are an inflammatory disease of the kidney, i.e. an acute or chronic glomerulonephritis, and malignant nephrosclerosis (Scherf and Boyd 12), and the only sign which deserves much attention and suggests prudence is the presence of diminished specific gravity of urine as a possible manifestation of renal insufficiency. Moreover, in recent times it has been proved that in most cases even of chronic nephritis there was no "evidence that the kidneys have been injured by the mercury " (Marvin 4), and some authors (Petersen, 13 Tursz, 14 and Pines 15) used successfully mercurial diuretics in the treatment of desperate anuria cases. In these latter instances the action of mercurial diuretics can be perhaps compared to the water treatment of Volhard 16 of some anuric or severely oliguric patients with acute glomerulonephritis in which the drinking of 1500 c.c. of water within one-half hour can force the existent renal block (Fishard 17).

Concerning the digestive tract the only true contra-indication is the presence of ulcerative colitis (Marvin 4). The really severe colitis with diarrhoea and bloody stools as the consequence of the administration of new mercurial diuretics is extremely rare and does not take place if the renal function is not impaired. A slightly increased number of stools following the injection, on the other hand, though perhaps a warning signal, is not by itself a contra-indication to the further use of the drugs. And stomatitis and excessive salivation according to Stokes 18 and De Graff and Nadler 19 are not always very reliable signs of mercurial intoxication and depend to the same extent " on the bacterial flora of the mouth and incidental conditions as on the dose of mercury that the patient is receiving.
MERCURIAL DIURETICS

Unfortunately, together with this recent evidence proving that the use of mercurial diuretics might be entirely safe in cases that previously were considered as not fit to receive even a small quantity of these drugs, new toxic reactions have been described, some of them connected with the drug itself and some with the diuresis that follows its administration. Moreover, some of these toxic reactions can be foreseen and eventually avoided or treated successfully; some of them, however, are unforeseeable and can lead to death in a most rapid and unexpected way.

Many of the alarming or even fatal reactions occur relatively late after the injection of the mercurial diuretic. This by itself indicates the existence of a stronger connection with the diuretic effect than with the mercurial diuretic itself. Fishberg 17 describes three fatal circulatory collapses developed between 8 and 14 hours after the intravenous injection of salyrgan to patients with coronary thrombosis. He attributes the fatal result to the sudden mobilization of a large amount of fluid into the blood stream with the exhaustion of the overburdened heart. Such an explanation is obviously open to certain doubts. The diuresis after the injection of mercurial diuretics starts relatively soon, about 2 to 3 hours after administration and ceases 9 to 21 hours afterwards. Taking into consideration the late occurrence of the fatal reaction and its peripheral character, it is more plausible to assume that the considerable dehydration and diminution of the circulating blood volume was the trigger mechanism of the collapse. Many authors mention dehydration and hemoconcentration, together with a negative chloride balance as a result of the administration of mercurial diuretic in spite of the persistence of edema (Degraff and Nadler 19). Some years ago Fournearo and Melleville 4 attributed, in an experimental study, the chronic intoxication following the use of mercurial diuretics to "some derangement in the animal’s water metabolism rather than to associated nephritis." Degraff and Nadler 19 point out that the deficiency of salt interferes with the excretion of water and can provoke the mercurial poisoning due to the incomplete elimination of the drug. The same authors quote Hines 10 as well as Evans and Paxon 21 as representing the opinion that azotemia appears rather as a consequence of the rapid elimination of great quantities of edema fluid than of the damage suffered by the kidneys from the mercury. Symptoms of chloride depletion are generally seen after the copious diuresis following mercurial diuretics. Sometimes these are relatively mild and the patients complain of weakness and of pains, particularly in the calf muscles. Other times a severe picture of great chloride depletion, comparable to heat prostration or pernicious vomiting with apathy, somnolence, severe mental symptoms, and eventually death, can develop.

Another type of alarming or fatal reaction following mercurial diuresis can be related to digitalis toxicity. Since 1931 there have appeared various studies indicating that the edema fluid of digitalized patients can contain large quantities of this drug and produce even toxic reactions when the edema fluid finds its way rapidly into the blood stream during mercurial diuresis. Biological methods were used in these studies and the authors have proved on hearts of frogs and cats that the edema fluid of digitalized patients is rich in digitalis or digitalis-like substance. Degraff and Nadler 19 point out that their experience is in accord with these studies and that symptoms of digitalis intoxication appear even when the patients had not received digitalis for several days. Personally we have seen many cases in which toxic symptoms have developed, which could be attributed to redigitalization depending on mercurial diuresis, and agree with them that some precautions must be taken before giving mercurial diuretics to fully digitalized patients. It is, however, worth while to stress that some authors consider that the evidence with respect to the redigitalization which occurs when the edema fluid enters quickly into the blood stream is not complete and that toxic symptoms can depend as well on many other factors, as for instance, the loss of large quantities of sodium base which gives rise to prostration or a shift of the acid-base equilibrium towards the alkalosis with all its symptoms, such as nausea and vomiting.

Finally a copious diuresis leads sometimes to the fall in serum sodium or calcium. A fall in serum calcium was noted by some observers and others have reported spontaneous tetany development after mercurial diuresis, though this latter was not always accompanied by the diminution of calcium in serum. Degraff and Nadler also mention that grand mal attacks have been attributed in epileptics sometimes to mercurial diuresis.

The careful analysis of other toxic symptoms or signs that appear after mercurial diuretics proves that some of them depend rather on the drug itself than on the diuresis, and that the causal mechanism of others is relatively uncertain. To this latter group belongs perhaps the delayed reaction as described by Wexler and Ellis 22 in the form of typical asthma attacks or pulmonary edema. Especially the pulmonary edema can be thought to depend on a great quantity of fluid entering rapidly into the blood stream and creating an unsupportable burden for the exhausted heart. Both their cases, which developed pulmonary edema 120 and 80 minutes respectively after the intravenous injection
of 2 c.c. of mercupurin, were in the state of cardiac failure, and this seems to speak in favour of such a comment. On the other hand, the pulmonary edema can be attributed to the toxic effect of mercury upon the heart muscle, and the bronchial asthma to a manifestation of an allergic reaction or of an idiosyncrasy.

Hypersensitive reactions are also well-known from other observations and appear in various forms. About two years ago Fox, Gold, and Leon \(^{23}\) described a case in which the injection of mercupurin and the administration of mercuric by rectal suppository, although the first 60 injections were well tolerated, led invariably to a severe reaction with fever, rash, nausea and vomiting, thoracic constriction, paresthesias, and swelling of the lips. The reaction developed invariably even when the dose of mercupurin was very small and contained only 4 mg. of mercury, although the second phase of this reaction consisted of signs characteristic of mercury poisoning, i.e. ulcerative stomatitis. The authors conclude rightly that the reaction was not dependent on the liberation of an ionized mercury, because there was no hypersensitiveness to other organic or inorganic mercury compounds, whose administration produced marked diuresis with only a negligible reaction or without any reaction at all.

In the same year Higgins \(^{24}\) described a similar case in which the hypersensitive reaction manifested itself one hour after an intravenous or intramuscular injection of mercupurin under the form of a severe chill, fever, dyspnoea, cyanosis, rapid fall in blood pressure and prostration, all of these symptoms and signs developing in rapid succession. The author points out he excluded the possibility of any cardiorespiratory lesion by the absence of any electrocardiographic evidence and by rapid disappearance of all these disturbances. According to him the fact that the reaction did not appear after three previous injections and that it bore some similarity to the reactions encountered after the administration of arsenicals supports the view that the reaction was of an anaphylactic type. He quotes some reported fatalities that occurred after intravenous injections of mercurial diuretics and not seeing any material difference between his experience and the reactions reported, suggests a new investigation of the toxicity of mercurial diuretics. He did not take into consideration apparently that the reactions described in other cases appeared only after the intravenous injection of the drug, that they manifested themselves much sooner after the injection had been effected, and that all available clinical evidence pointed to a cardiac character of such reactions described by other authors. Degraff and Nadler \(^{19}\) collected other hypersensitive reactions and mention among others, cutaneous eruptions in the form of urticaria, small reddish spots or purpuric areas, morbilliform and scarlatiniform erythema, chills, fever, and even reactions resembling a state of shock with sweating, cyanosis, collapse, and urinary suppression. They quote in this respect the investigations of Wilson \(^{26}\) who demonstrated by patch tests that these reactions may be of an allergic character and the observation of Parent \(^{20}\) that the individual susceptibility plays in the development of these reactions an important rôle.

All these reactions analysed above have been known for a long time, and have been connected with mercurial diuretics by all authors. Many times they could be foreseen or even avoided, and generally they appeared in lesser or greater degree independently of the route of administration. Moreover, the mechanism of these reactions is in many cases well known as was previously said. Also, the rôle of the kidneys in this respect has been thoroughly considered, and the contra-indications to the use of mercurial diuretics in some renal diseases precisely established. The same is true of the metabolism of salts and water, and it is well known that both of these factors must be carefully watched when mercurial or other diuretics are being given. With reference to redigitalization, there was always a certain difference of opinion, but in the main the diuretic mercurial is injected before the full digitalization of the patient is reached, or the quantities of mercurial are small, around 0-5 c.c., in order to avoid a violent reaction. Although hypersensitive reactions cannot be foreseen, even in these cases certain precautions can be taken by diminishing the initial dose of the drug, or by changing one preparation for another, or finally by adding certain substances like calcium gluconate to the mercurial diuretic before injection. Altogether, the known mechanism of reactions, the thorough analysis of contra-indications, and the precautions used in the injection of mercurial diuretics have brought about a relatively great degree of safety for the patients in the use of these drugs, and even when the reactions developed sometimes after the injection, they were of minor significance, and only extremely rarely alarming or fatal. There is, however, another type of toxic reactions appearing after mercurial diuretics that are completely different from all other reactions considered above, and the mechanism of which has only lately begun to be better understood and known.
The main features of this new type of reactions are as follows: (1) They manifest themselves in the clinic only after the intravenous route of administration, though there are certain suspicions in respect also to peritoneal route. (2) They appear very soon after the injection is over, generally from a few seconds to 5 or at most 10 minutes, and stop within a very short time if they are not fatal. (3) There is experimental and clinical evidence that these reactions happen because of disturbances in the specific heart musculature and perhaps also in the active musculature of the ventricles. (4) The peripheral vascular collapse was not observed during these reactions and, therefore, they are probably not of an anaphylactic nature (Wexler and Ellis). (5) The reactions are often severe and in great proportion they lead to immediate death. (6) Relatively small quantity of the drug or its high dilution does not always prevent the appearance of disturbances (Degraff and Nadler). (7) It seems that the reactions are more severe in the presence of considerable heart failure, though many of them have been described without heart insufficiency at all (cases of nephrosis). (8) They appear sometimes after the first injection, but sometimes also after the patient has received as much as 164 c.c. of mercupurin (Wexler and Ellis); sometimes all previous injections produce rather benign symptoms as in both fatal cases of Wexler and Ellis, or the previous injections are supported without any untoward symptoms as happened in Wilson's cases. (9) Sometimes all measures taken including epinephrine injections cannot prevent death (for instance, Carrillo's case), but sometimes epinephrine injections or other measures like morphine and oxygen seemed to be helpful (fourth case of non-fatal immediate reaction of Wexler and Ellis). (10) The reactions appear with particular frequency after esidrone and mercupurin injection, though sometimes the exchange of mercupurin for salyrgan does not prevent the reaction (first case of Barker, Lindberg, and Thomas).

This new type of toxic reaction after the intravenous administration of mercurial diuretics and in particular after mercupurin or esidrone seems so dangerous to everybody who has seen it (the senior author's 2 cases) that some authors are already demanding a re-examination of the whole subject of mercurial diuretics (Higgins and Friedfeld, Kissin, Modell and Sussman), some recommend great prudence in intravenous administration (Carrillo), and some recall that the diuretic response after intramuscular injection is often sufficiently abundant and that after intramuscular injection no fatalities as yet have been reported, or directly recommend the intramuscular route.

It is true that, as Wexler and Ellis point out, the frequency of severe or fatal reactions after the intravenous administration of mercurial diuretics is relatively low. In the reports available to us we find 26 cases analysed by Degraff and Nadler in 1942 beginning from Redlich's cases reported in 1926, i.e. for a period covering 16 years. To these must be now added 2 cases of Levin quoted by Carrillo, his own case, 2 cases seen by the senior of the authors, and 2 fatal and 5 alarming (immediate) non-fatal reactions encountered by Wexler and Ellis during 16 months in the Boston City Hospital. Though, perhaps, the statement of Degraff and Nadler in respect of the lowness of toxicity of mercurial diuretics as compared with the toxicity of arsphenamines still holds good, we do not believe that in the case of mercurial diuretics the state of the literature actually reflects the real toxicity of these drugs. This depends in part on the fact that the fulminant reactions have been known and understood only a relatively short time, in part because until ten or twelve years ago, the less toxic salyrgan and neptal were used instead of the more toxic novurit, esidrone, and mercupurin, in part because in the early years of mercurial diuretics intramuscular injections were used much more frequently than intravenous injections, in part because not all fatal reactions were attributed to the mercurial diuretics as the patients were in a very bad shape at the moment of injection, and finally in part because of unknown reasons.

The use of intravenous injections of mercurial diuretics in the treatment of heart disease is raising problems of increasing importance. Many authors (Fishberg, Levine) stress the efficiency of intravenous injections even when the intramuscular route does not give a
good diuresis, but already some hesitate very much before choosing this route. For example, Goodman and Corsaro \(^33\) refer to the toxicity of mercurial diuretics by intravenous injections, saying that only the intramuscular route was used in their study. Such an attitude is even more justified by the results of experimental studies.

After the initial experiments of Dresser \(^31\) in 1893, Mueller, Schoeller, and Schrauth \(^34\) described in 1911 an acute type of intoxication with mercury compounds which led to an immediate death in cats. In 1922 Salant and Kleitman \(^35\) performed their perfusion experiments with inorganic and organic mercury salts on a turtle heart and showed that a mercury compound independently of its anion produces disturbances of heart action particularly of the cardiac rhythm. The time at which these appeared depended on the concentration of the mercury salt, though when the experiment was carried on for long enough "delirium cordis" developed with dilutions as high as 1/10,000,000. They showed, too, that in dogs, "delirium cordis" resulted from the intravenous injections of inorganic mercurial salts and mercurochrome; and Salant and Kleitman's results with cats and dogs were similar to those obtained in more recent studies on the toxicity of organic mercury compounds. In 1923 Hatcher and Weiss \(^36\) attributed the emesis appearing after the intravenous injections of mercury chloride to direct reflexes from the heart. In 1926 Jackson \(^37\) studying the pharmacologic action of organic mercury compounds on the heart reported that 5 c.c. of a 2 per cent solution of salyrgan (about 100 mg. of salyrgan and 39.6 mg. of mercury) were producing regularly within 3 to 5 minutes the death of normal dogs through ventricular fibrillation. In 1929 McCrea and Meek \(^38\) proved that larger doses of mercury compounds produce pathological rhythms of the animal heart. In 1931 Fourneau and Mellville \(^9\) confirmed the results of Mueller, Schoeller, and Schrauth \(^34\) in respect of the "hyperacute fulminant" type of intoxication immediately after the intravenous administration of mercury compounds, but though "no definite lesions could be found in the central nervous system," they attributed the intoxication to the action on the central respiratory mechanism. In the same year Salant and Nagler \(^39\) when studying the effect of calcium and potassium on cardiac reactions to mercury, and making use of the isolated frog heart with Straub's method, found that mercury (bicloride) in concentrations above 1/500,000 in normal Ringer acted upon the conduction system as well as upon the active musculature of the heart producing the decrease of force and frequency of contractions and a certain irregularity of cardiac action; the cardiac resistance to mercury was considerably diminished in the hypodynamic heart, and also by interrupted treatment with mercury. After giving a solution 1/100,000 within about 30 minutes in certain experiments there was a progressive depression of the heart, whereas in others, the heart action was becoming weaker and irregular, extrasystoles and heart block manifesting themselves and persisting for a long time. The auricle was much more resistant against mercury than the ventricle, and calcium protected the heart from the toxicity of mercury compounds partially perhaps by decreasing permeability of cellular membrane, while potassium and mercury often showed synergism in their action upon the heart muscle.

The results of those older investigations have been fully confirmed by more recent studies. Chastain and Mackie \(^40\) in 1940 administering large intravenous doses of esidrone to normal dogs under barbiturate anaesthesia observed within 12 to 15 seconds after the injection deviation of the T waves, followed by ventricular flutter, fibrillation, and death. One year later Johnston \(^41\) showed similar results of intoxication with mercury salts, but added that the isolated turtle heart as well as the heart of the intact cat could recover if subjected to after-treatment with sodium thiosulphate. In 1942 Barker, Lindberg, and Thomas \(^37\) in an extensive study gave various mercurial diuretics intravenously to 30 normal dogs with and without intravenous barbital anaesthesia. Death was produced always by a particular pattern composed of depression of T waves, ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation. The results were exactly the same in the anaesthetized animals as in 4 vagotomized animals, in 2 animals with the cervical cord and both vagi severed, and in instances of an isolated perfused heart. From Fig. 1, 2, and 3 of their paper it is seen that the authors used in those experiments 2 c.c. of salyrgan, 2-2 c.c. of salyrgan and theophylline, and 1-4 c.c. of mercupurin. Otherwise the equivalent amounts of organic or inorganic mercury compounds were administered. The authors feel that "the mercury ion acts directly on the ventricular muscle to produce ventricular fibrillation and death."

In the same year another excellent study was presented by Degraff and Lehman,\(^42\) in which many pertinent data with reference to the acute toxicity of mercurial diuretics were firmly established. In experiments on cats and using the scheme similar to the proposed U.S.P.XII cat assay for digitalis the authors found the mean lethal dose for every mercurial diuretic frequently used by the medical profession. This mean lethal dose is the smallest for esidrone and greatest for salyrgan-theophylline, esidrone without theophylline, salyrgan, mercurin, and mercupurin occupying intermediary places...
between those two extremes. Moreover, they proved that the previous administration of digitaline, aminophylline, ammonium chloride, and soluble phenobarbital had no influence upon the mean lethal dose, and that even a slow rate of intravenous injection of mercurial diuretic to man did not give a guarantee against a lethal reaction. Some suggestions in respect to the slight protective action of a great dilution of the drug were also made, but one animal out of three died at a dilution of the drug as high as 1/25. Finally the conclusion was drawn that the lethal reaction is due exclusively to the cardiac action of the drug, the terminal event being ventricular fibrillation or respiratory failure depending on circulatory failure, and that the more gradual intravenous administration or the intramuscular injection of considerable quantities of mercurial diuretic produce successively the T wave changes accompanied by the fall of arterial and venous pressures, rapid ventricular tachycardia, and in case the heart does not recover, death through ventricular fibrillation or complete respiratory failure because of fall of arterial blood pressure. The authors also point to some experimental evidence that epinephrine can improve the heart poisoned by mercury, whereas ergotamine rather increases the toxicity of these drugs, and that the favourable influence of sodium thiosulphate and sodium formaldehyde sulfoxylate upon the heart disturbances provoked by the injection of mercurials must be further investigated.

In addition to these investigations Wexler and Ellis state that there is strong clinical evidence that in man the mechanism of lethal superacute or fulminant reaction to the intravenous injection of mercurial diuretics is exactly the same as in case of animals, and that “at present there is no known way of preventing fatal reactions.”

In conclusion, the mercuric ion liberated from organic mercurials produces abundant diuresis through its action upon the renal tubules, but simultaneously in certain doses, and if appearing rapidly in the blood stream of a mammal, it provokes serious disturbances in the conduction system of the heart as well as in the musculature of the ventricles. Previous research has established in general lines the mechanism of this phenomenon, but certain details are still lacking, and even more important no pertinent method has been indicated in order to avoid fatal or alarming reactions in man, especially when we are dealing with serious lesions of heart muscle. It seems of great urgency and importance, therefore, to find out if certain changes introduced in the chemical composition of mercurial diuretics or certain substances added or incorporated into them could prevent fatal reactions in human beings, and thus re-establish the safety of intravenous injections. If certain substances must be added to mercurial diuretics, to prevent fatal reactions they should, according to us, possess three other following qualities: viz., they should not diminish the diuretic qualities of mercurials but should if possible increase them by a synergistic action; they must be innocuous in the doses recommended; and finally, they must mix well with mercurial diuretics without forming a precipitate.

The search for such a substance or substances together with the effort to increase our knowledge in respect of the mechanism of fatal reactions was the principal purpose of the present study.

**METHOD**

Dogs were used for the present experiments. In all cases we applied general anaesthesia through the intravenous injection of pertinent amounts of somnifen Roche, because as was proved by Barker, Lindberg, and Thomas, the phenobarbital anaesthesia does not change the character of reaction due to injection of mercurial diuretics. Moreover, as the respiratory failure is only a secondary phenomenon and follows disturbances in heart action, artificial respiration was used in nearly all experiments. In a few, in which we did not open the chest of the animal and did not need, therefore, artificial respiration, the results were just the same as in all others. After the trachea was opened and artificial respiration applied, we proceeded in most experiments to open the chest in the usual way, trying to avoid all unnecessary hemorrhage. The pericardial sac was opened by a broad triangular dissection and its borders fixed to the chest walls. The disturbances of heart action were observed directly
and registered by means of electrocardiogram taken sometimes in the first, sometimes in the second lead, and sometimes in both. The Cambridge string electrocardiograph was used throughout.

The experiments consisted in partially intravenous and partially intracardiac injections of different amounts of esidrone. The injections were given sometimes into the cavity of the right auricle, sometimes into the cavity of the left ventricle or auricle, and sometimes into the jugular vein which was dissected beforehand and left free for this purpose. We were unable to observe any marked difference in the influence of esidrone upon the heart depending on the different place of injection. In the beginning by intracardiac or intravenous injection of 4 c.c. of esidrone we provoked the appearance of ventricular tachycardia followed within a few seconds by ventricular fibrillation. Later on, we convinced ourselves that the above-mentioned disturbances followed by a complete standstill of heart ventricles could be provoked in a dog of between 6 and 14 kg. of weight by an injection of only 2 c.c. of esidrone, though the ventricular fibrillation and complete heart standstill appeared a little later than by using 4 c.c. Nevertheless, the difference of time was only of seconds or of minutes, because even when 2 c.c. of esidrone were injected, the ventricular fibrillation appeared at most within 2 to 3 minutes after injection. At the end of the first phase of our experiments we injected intracardially or intravenously different amounts of 20 per cent solution of sulphate of quinine. This last drug not only did not hinder the appearance of ventricular fibrillation but it can be said that in all three experiments in which the sulphate of quinine was injected almost at once after the esidrone injection, ventricular fibrillation manifested itself at once, i.e. even earlier than was expected from previous experiments with esidrone. Later on we proceeded to inject magnesium sulphate after the full content of esidrone ampoule, i.e. 3 c.c. had been used. This method was changed for the simultaneous injection of magnesium sulphate with esidrone. In the beginning of the magnesium sulphate part of our study 2 c.c. of a 20 per cent solution together with 2-3 c.c. of esidrone were used tentatively. The dose of magnesium sulphate seemed too high, however, because, though the appearance of ventricular fibrillation was much delayed or did not produce itself, the cardiographic changes in respect of the disturbances of auriculo-ventricular and intraventricular conduction were even more marked than in the case of esidrone injection only. We observed also that when enough magnesium sulphate (10 c.c. of 20 per cent solution) was injected even after the esidrone was used, the heart would stop suddenly because of the complete cessation of its automatic function but without having passed through the phase of ventricular fibrillation. On the base of such and similar observations and reasonings the proper dose and timing of the magnesium sulphate injections were arrived at. In the last part of our experiments we were injecting the full amount of esidrone ampoule together with 0-5 c.c. of a 20 per cent solution of magnesium sulphate. The injections were effected with half-hour intervals between one another and no persisting heart disturbances were noted. Using this last method as many as seven times the lethal dose as established in previous experiments could be injected intravenously or intracardially and the heart still returned to the sinus though a little slower rhythm with disappearance of auriculo-ventricular and intraventricular block.

RESULTS

As already stated, we were able to confirm the experience of previous authors in respect of the unfavourable effect of certain doses of mercurial diuretics introduced rapidly into the blood stream upon the conduction system and the active musculature of the ventricles.

No effects upon the respiratory centre could be observed, however, because we were using artificial respiration, as we believe together with Degraff and Lehman that the changes in the respiratory centre during the course of fulminant intoxication with mercurial diuretics are completely secondary and depend in the first place on the fall of arterial blood pressure.
The doses administered to dogs chosen on the base of the mean lethal dose established for normal cats by Degraff and Lehman have proved themselves a little too high because those quantities of esidrone injected intracardially or even intravenously provoked ventricular fibrillation almost at once and did not permit observation of the course of intoxication. So, for instance, in one experiment the intracardiac injection of 4 c.c. of esidrone to a dog of 17 kg. produced immediately intraventricular block and a few seconds later irreversible ventricular fibrillation, although the lethal dose for this dog as calculated on the base of mean lethal dose established for cats by Degraff and Lehman would be 4-08 c.c. of esidrone (Fig. 1). In other experiments when we administered esidrone by the jugular vein—similar results were obtained. At the end of our first stage of experiments, therefore, we diminished considerably the dose of esidrone and injected dogs of even above 10 kg. with a quantity of esidrone which varied between 1 and 2 c.c. This was always enough to provoke the fulminant intoxication with ventricular fibrillation appearing within 2 to 5 minutes, thus enabling us to observe better all electrocardiographic changes. This agrees with Barker, Lindberg, and Thomas,27 who obtained ventricular fibrillation and death by injecting a dog of 7 kg. with a dose of mercurin not higher than 1-4 c.c., although according to Degraff and Lehman’s data for cats the lethal dose for this dog should have been 5-8 c.c. We have no other explanation for this fact than the possible influence of barbital anaesthesia used by us as well as by Barker, Lindberg, and Thomas in spite of the fact that these authors did not find proofs for the existence of such a difference, and also perhaps the fact that we were administering the full lethal dose at once, together with the difference between two species.

From this first part of our experiments two other facts are also apparent. The anoxia of heart muscle increases its sensitivity to intoxication by mercurial diuretics, as in two experiments in which the artificial respiration apparatus ceased to work because of some defect of its mechanism, ventricular fibrillation appeared at once, and thus much earlier than we could expect on the base of our previous experience with the same dose of esidrone. This perhaps can explain to some extent why a failing heart and in particular infarcted heart muscle seems to be more sensitive to mercurial intoxication (Fishberg 27).

Another fact which we observed concerns the development of intoxication. Degraff and Lehman,42 as well as Barker, Lindberg, and Thomas,27 describe a particular pattern of mercurial intoxication consisting of early changes of the T wave, followed by disturbances in intraventricular conduction, ventricular extrasystoles, ventricular tachycardia, ventricular flutter and fibrillation, and death. In some of our experiments, however, we were able to observe a more uniform action of mercurial diuretics upon the heart conduction system, as on a parallel line with T wave changes and intraventricular conduction defect, there appeared some disturbance of auriculo-ventricular conduction (Fig. 2). This agrees with the clinical
Fig. 2.—(A) Before injection of esidrone: normal rhythm; frequency 111 a minute; P–R, 0·03 sec.; QRS of small amplitude and 0·03 sec.; T negative, 2 mm. (B) After injection of 2·3 c.c. of esidrone: normal rhythm; frequency 115 a minute; P–R, 0·18 sec.; QRS broad, deformed, with S wave deep in form of staircase ("en marche d'escalier"), and 0·16 sec.; T positive, 3 mm. Simultaneous appearance of auriculo-ventricular and intraventricular conduction disturbances after esidrone.

observation of Wexler and Ellis, who in one case of rheumatic heart disease with auricular fibrillation mention the appearance of periods of complete heart block with a ventricular rate around 50 during acute intoxication with mercurial diuretics.

From the first part of our study it seems that sulphate of quinine not only has no hindering effect upon the development of ventricular fibrillation in the course of intoxication with mercurial diuretics, but on the contrary rather accelerates it, as is well seen from Fig. 3A, B, and C, where the administration of 0·25 g. of sulphate of quinine has, if anything,

quickened the mercurial reaction. This effect of quinine and quinidine especially in greater amounts is well known from experience with even healthy heart muscle (Boyd and Scherf, Goodman and Gilman).

From the second part of our experiments the conclusion must be drawn that magnesium
mercurial diuretics. This tendency is well seen from one experiment, in which 10 c.c. of a 20 per cent solution administered within 2 minutes after the injection of 0-5 c.c. of esidrone and in a moment when disturbances of intraventricular conduction had already manifested themselves, hindered the appearance of ventricular fibrillation, though the action of the heart ceased suddenly after the short period of considerable disturbances in auriculo-ventricular and intraventricular conduction. The possibility of a kind of synergistic action of magnesium sulphate and of mercurial diuretic in toxic doses upon the conduction system of the heart induced us to diminish greatly the dose of magnesium sulphate and in order to assure a favourable effect, we began to inject this last substance simultaneously with esidrone. In these latter experiments we observed a very favourable action of 0-5 c.c. of a 20 per cent solution of magnesium sulphate upon the course of heart intoxication due to intracardiac or intravenous injection of esidrone. Thanks to this suppressive action of magnesium sulphate in the dose mentioned, we could administer up to seven times the dose which we have every reason to consider as lethal, without any persisting ill effects upon the heart action. This does not mean that 0-5 c.c. of a 20 per cent solution of magnesium sulphate always and totally arrested the reaction due to the administration of a mercurial diuretic in the dose known as lethal. Sometimes the disturbances of the conduction system did not manifest themselves at all after the first dose of 2-3 c.c. of esidrone. Sometimes they did, however, and always appeared after the second 2-3 c.c. dose of esidrone. But they never continued and the heart of the animal after a certain time, generally less than 30 minutes, returned to sinus rhythm, though often slower than before, the ventricular complexes acquiring normal aspect and the T waves returning nearly to their previous shape.

![Reprinted from Br Heart J: first published as 10.1136/hrt.6.4.197 on 1 October 1944. Downloaded from http://heart.bmj.com on July 5, 2021 by guest. Protected by copyright.](http://heart.bmj.com/)

**Fig. 4.—Repeated injection of esidrone. All lead I.** (A) Before injection of esidrone: sinus rhythm; frequency 143 a minute; P–R, 0-10 sec.; QRS, 0-05 sec.; T positive, 1 mm. (B) Normal appearance after injection of 2-3 c.c. of esidrone and 0-5 c.c. of a 20 per cent solution of magnesium sulphate. (C) The same within 5 minutes after the second injection of the same combination of drugs. (D) After third injection of esidrone and magnesium sulphate: sinus rhythm; frequency 143 a minute; P–R, 0-12 sec.; QRS, 0-12 sec.; T positive, 2 mm. (E) Electrocardiogram returning to its normal aspect within 5 minutes after third injection of esidrone and magnesium sulphate. (F) After sixth injection of 2-3 c.c. of esidrone and 0-5 c.c. of a 20 per cent solution of magnesium sulphate. Complete heart block and atypical ventricular complexes. Auricular frequency 130 a minute. (G) After seventh injection of esidrone and magnesium sulphate: sinus rhythm; frequency 49 a minute; P–R, 0-24 sec.; QRS, 0-08 sec.; T diphasic.
To illustrate better this influence of magnesium sulphate we should like to describe with more detail the course of one of these last typical experiments. The weight of the dog was 12 kg. After a deep anaesthesia, induced through the intravenous injection of 10 c.c. of somnife, we proceeded to artificial respiration and chest opening in the above described way. The pericardial sac was opened and fixed to the chest borders. The cardiogram is normal in all respects, the heart frequency being 142 a minute (Fig. 4A).

The first injection of 2.3 c.c. of esidrone +0.5 c.c. of a 20 per cent solution of magnesium sulphate did not produce any appreciable changes during half an hour of observation. The second injection of the same combination of drugs, on the contrary, produced the appearance of intraventricular, though not very intensive, conduction defect. Moreover, these intraventricular conduction disturbances lasted for only a very short time, ceasing completely after about 5 minutes, when Fig. 4C was taken. The third injection produced more intraventricular conduction defects accompanied by prolongation of P-R, but even this time the cardiogram returned within 5 minutes to its normal (Fig. 4E). The following fourth, fifth, and sixth injections produced even more accentuated changes in the intraventricular and auriculo-ventricular conduction including complete auriculo-ventricular block and a few times an atypical ventricular complex, but invariably after perhaps a little more time, although well below half an hour, sinus rhythm was re-establishing itself (Fig. 4G). At the end, after 5 hours, the experiment was interrupted without the appearance of ventricular fibrillation.

All experiments done in the same way gave similar results, although sometimes we could induce ventricular fibrillation by repeating at small intervals of time the injections of a dose as high as 4 c.c. of esidrone. The conclusion was drawn, therefore, that magnesium sulphate has a hindering effect upon the ventricular fibrillation due to intoxication of mercurial diuretics, though it does not suppress the ill effects of the injections of excessive doses and generally does not hinder the appearance of some disturbances in the auriculo-ventricular or intraventricular conduction.

COMMENT

From clinical observation and from experiments upon animals, confirmed also by this study, we can now reconstruct the influence of the mercurial compounds upon the heart muscle. In certain doses they are powerful depressants for the whole of the heart muscle. This action is much weaker upon the higher segments of the heart but increases rapidly beginning from the A-V node. In this respect we can confirm Salant and Nagler, who have proved that the auricle was much more resistant to mercurial compounds than the ventricle, and the recent observations of Barker, Lindberg, and Thomas, that after the ventricular electrical impulses have stopped, the auricles continued to beat in a regular sinus rhythm. We had the opportunity to observe the same phenomenon many times. This does not mean, however, that the mercurial compounds have no influence upon the S-A node or upon the auricular muscle. Simultaneously with the appearance of complete heart block nearly always a small decrease of the auricular rate, and therefore, a slight decrease of the frequency of impulse formation in the S-A node, could be noted. After recovery from mercurial intoxication a slower sinus rhythm is the rule according to the investigations of ourselves and other authors (Degraft and Lehman). This recalls to some extent the direct influence of quinidine upon the S-A node.

The depressive influence of mercurial compounds upon the A-V node is, however, much stronger, as in the case of quinidine or quinine. It was recorded by us many times in the form of latent, partial, or complete heart block and was confirmed by Wexler and Ellis’s clinical observation of periods of complete heart block during the recovery from mercurial toxic reaction in a case with auricular fibrillation. Moreover, this depressive action of mercurials upon A-V conduction explains also the mechanism of the appearance of the bundle branch block. According to Pines it can be always questioned whether the asynchronism of contraction of the ventricles is caused by the acceleration of conduction in one bundle branch or its slowing in the other, unless there is strong evidence that we are dealing with a phenomenon or a drug which has a depressing action upon various segments of the conduction system. In the case of mercurials such evidence seems to be furnished by their influence upon A-V conduction.
MERCURIAL DIURETICS

It is more difficult to explain the mechanism of changes in the T waves recorded by all authors who have studied the mechanism of hyperacute intoxication provoked by mercurial compounds. There was a relatively old report of Jackson 37 that salyrgan acts on the heart through the stimulation of the vagi and that as soon as the vagus control is removed, death ensues, not because of heart failure but because of paralysis of the respiratory centre. On the other hand, as we know from the studies of Samojloff 46 and Rothberger and Winterberg 47 that the vagus stimulation produces T waves of small amplitude, the T wave changes occurring in the early stage of mercurial intoxication might depend on the stimulation of the vagus nerve. This explanation is, however, not very probable. Jackson 37 did his experiments on dogs under ether anaesthesia. Kobacker and Rigler, 48 on the other hand, found on cats in 1929 that ether anaesthesia paralyses the vagus nerve. The same was known from Ruttger's 49 experiments on the heart of the frog. Moreover, Steinfeldt 50 proved that the pulse frequency increases during ether anaesthesia, and Rothberger 51 observed that the respiratory arrhythmia due to the central excitation of vagus and so well marked in the morphinized dog, disappears immediately after the beginning of the ether anaesthesia. Finally, Pines, 52 in 1934, demonstrated that this effect depends not so much on the diminution of the effect of acetylcholine, but rather on the partial or complete arrest of the secretion of vagus substance. On the basis, therefore, of these experiments the results obtained by Jackson 37 are open to certain doubts. And still more so because Salant and Kleitman, 35 as well as Barker, Lindberg, and Thomas, 27 demonstrated directly by means of bilateral vagotomy or atropinization that the suppression of the influence of the vagus nerve does not change the action of mercurials upon the heart. The changes of the T waves recorded during the early stages of intoxication with mercurials must be, therefore, attributed rather to the toxic effect upon the active musculature of the heart which is known from the experiments of Salant and Nagler, 39 among others, particularly that the increase of strain on either or both ventricles does not enter into consideration before the mobilization of the peripheral fluid has time to occur.

Concerning the ventricular fibrillation reported and observed by all authors as well as by us as the final result of an acute mercurial intoxication, very little need be added. It is well known that many myocardial depressants and myocardial stimulants alike can produce ventricular fibrillation. Even quinidine itself, which has certain value in preventing and alleviating ventricular fibrillation, when administered in excessive doses results in ventricular fibrillation in experimental animals (Katz 53). Mercurial compounds probably act in a similar way. As a matter of fact we have found a certain synergism between the influence on the heart of large doses of quinine and of mercurial compounds in the later stages of acute mercurial intoxication.

The action of magnesium sulphate in preventing the lethal effects of acute intoxication with mercurial diuretics, must, on the other hand, be considered separately as it is of considerable importance, practically and theoretically.

Magnesium is apparently indispensable for life of the mammals and plants (Goodman and Gilman 7). Its concentration in human serum is according to current opinion between 2 and 3 mg. per 100 c.c., and in red corpuscles about 4 mg. It is interesting to note its high concentration in cardiac muscle and its fall in cases of cardiac failure. According to Harrison 44 the left ventricle of the normal cardiac muscle contains about 20 mg. of magnesium, whereas the same ventricle of patients who died from congestive heart failure contained only 16 mg. of magnesium per 100 g. of fresh tissue. Pharmacologic properties of magnesium salts have been studied for a long time. Smith, Winkler, and Hoff 66 mention in their paper that the results of their investigations in respect of the action of magnesium on the mammalian heart are in agreement with older experiments of Hay 46 effected in 1882 and relatively more recent investigations performed by Matthews and Jackson 57 in 1907. With reference to the influence of magnesium sulphate on the mammalian organism there was particularly fruitful research connected with the efforts of Meltzer and Auer 58 and of other authors in order to introduce this drug for general and local anaesthesia. It has been found that parenteral administration of magnesium sulphate induces general anaesthesia (Meltzer and Auer); that there is a certain synergism between the action of magnesium salt and ether or morphine.
(Gwathmey and others); that the solution of magnesium sulphate paralyses the exposed motor and sensory nerves (Meltzer and Auer, Liljestrand, and Guthrie and Ryan); that the chief danger of parenteral administration of magnesium sulphate consists primarily in the paralysis of respiration due in cases of moderate doses mainly to the curare action, and that only much greater quantities can produce cardiac arrest due to well known cardio-inhibitory action of magnesium; that magnesium sulphate can be useful in the symptomatic treatment of tetanus (Kocher; Meltzer) and against strychnine and other convulsants; that after the magnesium sulphate anaesthesia there can appear some diuresis together with cylindruria and glycosuria. Later on the magnesium sulphate was recommended for the treatment of asthmatic crises and of endarteriitis obliterans as well as for certain diagnostic and therapeutic procedures like estimation of circulation time or duodenal drainage (Meltzer and Lyon test).

According to Boyd and Scherf the first effort to use the cardio-inhibitory properties of magnesium for the treatment of heart disturbances is due to Seekles, who administered magnesium chloride intravenously to eliminate arrhythmias depending on the injection of calcium chloride into cows suffering from milk fever or grass staggers. But the real interest in these properties of magnesium was only evoked when Zwillinger recommended in 1935 the intravenous injections of 10 c.c. of a 20 per cent solution of magnesium sulphate for the treatment of paroxysmal tachycardia and ventricular premature beats or ventricular flutter. One year later Rothberger and Zwillinger, in very extensive animal experiments succeeded in preventing or eliminating the ventricular tachycardias caused by barium or by digitalis previously known as irreversible. Rothberger pointed out with insistence that the property of arresting the otherwise irreversible digitalis or strophantine ventricular tachycardias is unique and characteristic for magnesium sulphate, the inhibitory action of which is much more strong upon the ectopic pacemakers than upon the S-A node.

The cardio-inhibitory action of magnesium salts was also studied not long ago by Smith, Winkler, and Hoff. They proved that its chief action on the heart consists in the general depression of conduction, i.e. depression of sino-auricular, auriculo-ventricular, and intraventricular conduction, the action upon this latter being, however, not so extreme as to provoke the disorganization of the whole ventricular complex, as in case of potassium. The recommendation of Zwillinger to use magnesium salts in order to prevent ventricular flutter and extrasystoles, on the other hand, has been found to be based on scant physiological evidence because such arrhythmias could be induced or appeared spontaneously in the presence of greatly increased concentration of magnesium in the serum.

The clinical evidence, however, presented in the recent paper of Boyd and Scherf confirms entirely the experience of Zwillinger and of Rothberger and Zwillinger, and seems to indicate the usefulness of intravenous administration of a 20 per cent solution of magnesium sulphate in cases of paroxysmal auricular and ventricular tachycardia.

The results of our study also confirm the views of Zwillinger, Rothberger and Zwillinger, and Boyd and Scherf. We have convinced ourselves that the addition of small quantities (0.5 c.c.) of a 20 per cent solution of magnesium sulphate to the intravenous or intracardiac injection of a lethal dose of mercurial diuretic prevents ventricular fibrillation and death of the animal, although particularly after the second and following injections it does not prevent the development of some disturbances of conduction. This is especially marked when the magnesium sulphate in this small dose is given simultaneously with mercurial diuretic. In this way one is able to inject with relatively small intervals of time (about half an hour) doses as much as 7 to 8 times higher than the dose known as lethal for normal dogs, and no persisting harmful effects are apparent. Even when magnesium sulphate is given after the injection of the mercurial diuretic in a lethal dose, it has analogous effect, because it arrests the heart without the phase of ventricular fibrillation, as we had the opportunity to observe a few times.

There seems to be no direct contradiction between the results of our study and those obtained by Smith, Winkler, and Hoff. Many other drugs which in certain conditions are capable of preventing or alleviating ventricular fibrillation, in excessive doses can produce
ventricular fibrillation in experimental animals (Katz 55). This refers to quinidine, potassium salts, and even to stimulation by faradic current. Boyd and Scherf 43 also mention this paradoxical double influence of cardio-inhibitory drugs and by it explain the frequent appearance of ventricular extrasystoles after the intravenous injection of magnesium sulphate. It is clear, therefore, why magnesium sulphate did not suppress ventricular fibrillation in Smith, Winkler, and Hoff’s experiments when the magnesium content of the serum reached an extraordinarily high level of 36 mg. per 100 c.c., although the inhibitory function of this drug upon the stimulus formation can in other conditions, whether clinical or experimental, be so obvious.

The mechanism of this protective action of magnesium sulphate upon the development of ventricular fibrillation in the course of acute intoxication provoked by the intravenous or intracardiac injection of organic mercurial diuretic is not known. A faint suggestion in respect of this mechanism can be looked for, however, in the fact that the injection of magnesium with the mercurial diuretic is more efficient than when it follows the injection of the mercurial diuretic at even only relatively very small interval of time. Some years ago Salant and Nagler 89 attributed the decreased toxicity of mercurial ion for the isolated heart produced by great doses of calcium, to the diminished permeability of the cell membrane. An analogous action of magnesium is known from the study of the nervous system and was brought to the fore by Moore 69 to explain its analgesic rôle. Possibly, therefore, this property of magnesium together with its inhibitory action are responsible for the protective influence offered by it in cases of acute intoxication by mercurial diuretics. Independently, however, of the exact details of this mechanism magnesium sulphate in pertinent doses and injected simultaneously with the mercurial diuretics, seems according to our study to correspond with our first postulate as mentioned in the introduction of this paper, i.e. to exert a protective action on the heart in the course of an acute intoxication by mercurial diuretics.

On the other hand, magnesium does not only not suppress the diuretic activity of mercurial diuretics, but rather increases the diuretic effect of organic mercurial compounds. A certain diuretic property of this drug was known already to Meltzer and Auer,58 who noted that after anesthesia with magnesium sulphate there is some diuresis but not diarrhea. White 76 in the new edition of his book, lists also magnesium sulphate among diuretics with no very strong diuretic properties when given alone. It is possible that this diuretic action is due mainly to the presence of the sulphate anion in magnesium sulphate molecule, which anion being rejected by the renal tubule is a powerful osmotic diuretic (Goodman and Gilman 7). Particularly clear is the diuretic activity of magnesium sulphate when administered together with mercurial diuretics. The senior of the authors many years ago used to inject intramuscularly a mixture of organic mercurial compound with 2 to 3 c.c. of a 20 per cent solution of magnesium sulphate, and observed beautiful diuretic responses. The theoretical reason for use of such a mixture was the Elias 31 hypothesis that diuretic mercurials are initially excreted in bile, and only when re-absorbed from the digestive tract produce their diuretic action. All drugs, therefore, capable of increasing the secretion of bile as, for instance, decholin or perhaps also magnesium sulphate had to be considered according to this hypothesis as provided with synergistic properties in respect of the mercurial diuretics. An analogous mixture, but with much greater content of magnesium sulphate and with the addition of 1.5 c.c. of a 5 per cent procaine hydrochloride, was used for intramuscular injections by Shelling and Tarr,72 and Marvin 4 expresses the belief that there can be no question “that this combination is sometimes remarkably efficacious with patients who have shown little or no response to salyrgan.” Thus magnesium sulphate fulfils the second of our postulates to the effect that injected simultaneously it increases diuretic properties of mercurial diuretics.

Finally, the intravenous injection of such small quantities of magnesium sulphate (0.5 c.c. of a 20 per cent solution) together with mercurial diuretic seems to be completely safe. Boyd and Scherf 43 employed in their series the injection of a 20 per cent solution in amounts from 10 to 20 c.c., even for cases with coronary sclerosis or myocarditis, and no “untoward effects have been observed.” They quote the observations of other authors according to which magnesium salts have been given in concentration from 10 to 30 per cent to patients with coronary sclerosis, angina pectoris, etc., without any alarming reaction. Magnesium sulphate in a concentration as high as 42 per cent, though with the addition of calcium gluconate, has been also used many times for the estimation of circulation time, apparently without ill effects. The same refers to dogs, because Moore and Wingo 74 injected their dogs with large doses of
magnesium chloride, and when the injection was stopped before the occurrence of the respiratory arrest some animals survived without permanent injuries although the blood Mg level reached 20 to 24 mg. per 100 c.c. Schmidt and Greenberg estimate the fatal dose of MgSO$_4$.7H$_2$O for a dog with normal serum calcium as between 0-23 and 0-28 per kg. We have injected our dogs of a weight of around 10 kg. with 0-5 c.c. of a 20 per cent solution or 0-1 g. of magnesium sulphate, or 0-01 g. per kg. The therapeutic index (relation between fatal and effective dose) was therefore on the base of these data 25 : 1.

The assumption is justified, therefore, that the doses of magnesium sulphate employed by us are completely safe for dogs and particularly for man, and that magnesium sulphate fulfils the third of our postulates, i.e. it is absolutely safe in the doses recommended. We believe that incorporation of small quantities of magnesium sulphate into the solution of mercurial diuretics should be made in order to prevent fatal reactions resulting from intravenous injection of these drugs: in addition, magnesium sulphate mixes with mercurial diuretics without forming any precipitate.

**SUMMARY**

The course of acute intoxication produced by the intravenous or intracardiac injections of Wisdrone was studied on normal dogs with the help of the electrocardiograph. It is concluded in agreement with other authors that mercurial diuretics in certain doses are general depressants for the whole cardiac muscle. The following pattern of intoxication was observed: changes of T waves, intraventricular and auriculo-ventricular conduction disturbances, diminution of frequency of impulse formation in S-A node, ventricular paroxysmal tachycardia, chaotic heart action, ventricular fibrillation, and death.

The addition of small quantities of magnesium sulphate (0.5 c.c. of a 20 per cent solution) prevents ventricular fibrillation and death, even if doses 7 times higher than normal lethal doses are used. Magnesium sulphate, however, does not prevent and even perhaps increases the conduction disturbances resulting from the administration of lethal doses of mercurial diuretics. On the other hand, such amounts of magnesium sulphate increase the diuretic response, are entirely safe, and mix with mercurial diuretics without forming any precipitate.

It is suggested that small quantities of magnesium sulphate be incorporated into the mercurial diuretics in order to prevent fatal reactions resulting sometimes from the intravenous injections of these drugs.

**REFERENCES**

Owing to the arrangement of this paper, it has been thought best to make an exception to the usual custom and to leave the references in the form presented by the Author, except that the year where given is put after the author’s name.—EDITOR.

14. Tursz: Personal communication.
29. Redlich: quoted by Degraff and Nadler (19).
30. Levin: quoted by Carrillo (45).
34. Mueller, Shoeller, and Schrauth: quoted by Fournier and Melville (9).
35. Salant and Kleitman: quoted by Wexler and Ellis (22).
37. Jackson: quoted by Wexler and Ellis (22).
38. McCreary and Meek: quoted by Sollmann (75).
49. Rutger: quoted by I. Pines (44).
50. Steinfeild: quoted by I. Pines (44).
51. Rothberger: quoted by I. Pines (44).
57. Matthews and Jackson: quoted by Smith, Winkler, and Hoff (55).
58. Meitner and Auer: quoted by Sollmann (75).
60. Lijestrand: quoted by Sollmann (75).
61. Guthrie and Ryan: quoted by Sollmann (75).
62. Kocher: quoted by Sollmann (75).
63. Meitner: quoted by Sollmann (75).
64. Meitner and Lyon: quoted by Sollmann (75).
65. Seckles: quoted by Boyd and Scherf (12).
67. Rothberger and Zwilling: quoted by Endelman and Pines (see 66).
68. Rothberger, C. J.: Personal communication.
71. Elias: Personal communication.
72. Shelling and Tarr: quoted by Marvin (4).