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Acute Toxicity of Some Mercurial Compounds for the Circulation on Intravenous Injection.

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From the toxicological point of view, the 2 most important organs undergoing pathological changes in mercurial poisoning are the kidneys and the intestines, both exhibiting severe inflammatory and degenerative changes. It is well known, however, that the mercury ion produces a depressant effect on the circulation. According to Sollmann,[1] all metals produce a very marked fall of blood pressure, which is partly due to the paralysis of the blood vessels and partly to a direct action on the heart. The metals, for this purpose, may be divided into 2 groups, one group acting mainly peripherally on the blood vessels and the other group acting mainly peripherally on the heart. Mercury belongs to the latter group.

The writer has studied for some time the toxic effects on the circulation, and especially on the heart, of continual intravenous injections of various mercurial compounds, and the results, of considerable toxicological and practical interest, are here reported. The method of experimentation was simple. All the experiments were performed on cats and the technique followed was similar to that employed in the assay of digitalis by the Hatcher-Brodie cat method. The animals are kept under light ether anesthesia and a solution of a given mercurial is injected into the femoral vein from a burette at regular intervals, usually at the rate of 1 cc. a minute, and the effects upon the heart are carefully observed. When the inorganic salt, mercuric chloride, or bichloride of mercury, in concentration of 1:1000, is thus injected into the vein of a cat, the depressant effect of the mercury for the heart is manifested after a few minutes. Even after the injection of a small quantity of the solution, the heart-beat becomes feeble and the heart rapidly develops a block, after which, on continued injection of the drug, it goes into fibrillation and finally stops. The author found that the lethal dose required to produce arrest of the heart by such continual injections of mercuric chloride (1:1000, at the rate of 1 cc. a minute) is 30 mg. per kilo weight of the animal. If, however, a considerable quantity of blood is first removed from the animal and this blood

[1] Sollmann, T., Manual of Pharmacology, second edition, 1922, 856.

is replaced with an equivalent amount of physiological sodium chloride solution, the minimal lethal dose is even less, namely, about 15 mg. per kilo weight of the animal. This difference is probably due to the partial binding of the inorganic mercury by the blood proteins in case of the non-exsanguinated animal.

A solution of mercury benzoate, prepared by dissolving this compound in solution of 0.45% of sodium chloride was injected into cats by the above method and the lethal dose was also found to be very small, 38 mg. per kilo weight of cat producing arrest of the heart and death. An examination of still another inorganic compound gave quite a different result. Mercuric iodide, or "red iodide" of mercury, is practically insoluble in water but it can be dissolved in a solution containing approximately its weight of sodium iodide. When such a solution of mercuric iodide, in concentration of 1:1000, was injected into the vein of a cat, it was found to be much less toxic than the mercuric chloride or the mercury benzoate, the lethal dose being 125 mg. per kilo weight of the animal. This great difference in toxicity between the bichloride and the iodide of mercury solutions is undoubtedly due to the difference in their manner of dissociation. The bichloride dissociates, yielding mercuric ions; the "red iodide" of mercury forms a double salt with the sodium iodide and when this double salt is dissociated, it does not yield free mercuric ions to any appreciable extent. It may be well to add that sodium iodide and the iodide ion alone have been shown long ago by the author not to be depressant for heart muscle.[2]

A series of organic chemical compounds were also studied toxicologically in the manner described above. The compounds examined were oxi-mercuri-di-brom fluorescein, or mercurochrome-220 soluble, the di-mercury form of mercurochrome; mono-mercuri fluorescein, or flumerin; and mono-hydroxy-mercuri-di-iodo-resorcin-sulphon-phthalein, a new compound recently described by Dunning and Farinholt.[3] The results are exhibited in Table I. It will be noted that, when studied on the circulation, all the organic compounds were much less toxic than the inorganic compounds of mercury (with the exception of the mercuric iodide), thus indicating that the mercury in these compounds is in firmly bound organic combination and not easily broken up in the blood stream in such acute experiments as are under discussion in the present investigation. These findings are of considerable practical interest. The author has had occasion to examine various specimens of spurious

[2] Macht, D. I., *Johns Hopkins Hosp. Bull.*, 1914, **25**, 278.

[3] Dunning, F., and Farinholt, L. H., *J. Am. Chem. Society*, 1929, **51**, 804.

substitutes for oxi-mercuri-di-brom fluorescein, or mercurochrome-220 soluble, and has found the present method valuable in detecting inorganic mercury in such solutions. Thus it will be seen from the table that when mercuric chloride, 1:5000, is added to the solution of mercurochrome, 1:200, the toxicity of such a mixture for the cat's heart is much greater than that of pure mercurochrome. Even one part to ten thousand of bichloride can also be detected in this way. This method, unfortunately, does not apply to the detection of mercuric iodide when added to mercurochrome solutions but in such cases a very simple chemical examination can readily establish the presence of an iodine compound in the preparation, on the one hand, and of inorganic mercury, on the other. Practically no difference was noted in the toxicity of the organic mercurial compounds between exsanguinated and non-exsanguinated animals.

TABLE I. *Toxicities for Cats.*

Compound	Concentration injected, 1 cc. a min.	Lethal Dose mg. per kilo
Mercuric chloride (after previous bleeding)	1:1000	15
Mercuric chloride (without previous bleeding)	1:1000	30
Mercury benzoate (in NaCl solution)	1:1000	28
Mercuric iodide ("red iodide" in NaI solution)	1:1000	125
Oxi-mercury-di-brom fluorescein (mercurochrome-220)	1:200	150
Di-mercury-mercurochrome	1:200	140
Mono-hydroxy-mercuri-di-iodo-resorcin-sulphon-phthalein (merodicein)	1:500	200
Mono-mercuri-fluorescein (flumerin)	1:200	140
Mixture of { mercurochrome	1:200	{ 104
Mixture of { mercuric chloride	1:5000	{ 5

Summary. 1. Continuous intravenous infusion of solutions of mercurials in cats produces depression of the heart muscle, heart block and arrest of the heart. 2. There is an enormous difference in toxicity between organic and inorganic mercury compounds in this respect, the inorganic mercurials being much more toxic owing to the free play of the mercury ion in the solutions. 3. Solutions of mercuric iodide in sodium iodide are an apparent exception to the rule because of the formation of a double salt of mercury and sodium iodide and the peculiar dissociation of this compound in solution. 4. This effect of mercurials on the circulation is useful in the detection of inorganic mercurials which may be mixed with solutions of true organic mercury compounds.