

there was no mark at the point of inoculation. Cultures from the brain and blood yielded a pure growth of the green-producing streptococcus. The spinal fluid in tall tubes of ascites meat infusion and meat infusion yielded a pure culture of a pleomorphic short-chained streptococcus. When a week old, this culture was transferred to glucose-brain broth, and the twelve hour growth in this medium was inoculated into two rabbits, one receiving 0.1 c.c., the other 0.1 c.c. of a 1:1,000 dilution. The findings in the two rabbits were almost identical. Those of the first are sufficiently illustrative.

A rabbit, weighing 2,000 gm., was injected intracerebrally, April 2, 1922, with 0.1 c.c. of a glucose-brain-broth culture of the streptococcus from the spinal fluid in the second culture generation. April 3, at 10 p. m., the respirations were somewhat increased, but the animal did not have spasms. April 4, at 7 a. m., the respirations were greatly increased. The animal was restless and uncomfortable, and when made to hop became markedly tremulous, and the muscles over most of the body twitched; at times this almost amounted to a universal clonic spasm. At noon the condition was about the same. Spasms of the extremities and of the muscles of the back were repeated rapidly. At 6 p. m., the condition was unchanged. April 5, at 8 a. m., the respirations were still markedly increased. The animal was hyperesthetic and excitable, and had repeated attacks of general twitchings of the muscles, especially those of the fore extremities. When it was forced to hop, the spasms extended to the hind extremities, became quite violent, and threw it around. At 10:15 it was found lying on its side with continuous tremor and twitchings of the masseter muscles, and the muscles of the neck, shoulder, back and fore extremities; at intervals it had clonic twitchings of the hind extremities. These increased greatly on prodding. A little later the animal died, and was examined at once.

The vessels of the meninges were moderately congested; the spinal fluid was slightly turbid; there were no gross lesions at the point of injection, none in the brain or the cord elsewhere, and none in the viscera. The blood was sterile, and cultures from the brain yielded a pure growth of the organism injected.

Sections of the brain and cord of this rabbit showed a variable degree of leukocytic and round-cell infiltration of the meninges, perivascular spaces, and substance of the brain and pons remote from the blood vessels. The proportion of leukocytes and round cells varied with the duration of the experiment. The character of the lesions found in the animals injected with the strain from the nasopharynx and in those injected with the strain isolated from the spinal fluid was identical (Figs. 2 and 3).

On account of the striking improvement in the patient following the injection of the encephalitis serum, a protection experiment with this serum was made in rabbits. Six rabbits of approximately the same weight were selected and divided into three groups of two each. All were injected intracerebrally twice, twenty-four hours apart, with 0.1 c.c. of a 1:1,000 dilution of the glucose-brain-broth culture of the streptococcus isolated from the rabbits injected with the salt solution suspension of the pus from the tonsils. The serum was given to four of the rabbits, two receiving it at the time of each injection of the bacteria, two the day before the injection and also at the time of each injection. The two that were not given the serum were found dead the morning after the second injection. One of the two given simultaneous intravenous injections of 1 c.c. of the serum died late on the second day, the other on the fourth day after the second injection. One of the two given 1 c.c. of the serum intravenously the day before and 1 c.c. with each injection of the culture died on the fifth day, and the other survived. The latter remained well until the third day, when it developed a peculiar motion of the head, throwing it from side to side and occasionally backward. These movements, which were always worse when the animal hopped and when it was prodded, gradually grew less, but were still noticeable three weeks later when it was chloroformed. Cultures from the brain and the cord were negative.

COMMENT

The effect of the injection of serum in all three cases was so striking that it seemed advisable to report this small group, with the hope of interesting others in the specific treatment of encephalitis, in order to determine whether the same excellent results can be obtained in a larger series of cases. The experience of any one man with acute encephalitis is rather limited, but the number of cases is large in the aggregate, and we are anxious that the serum shall be tried out in a larger number of cases. It is available to all who are interested in using it.

We do not claim at present that the specific serum was the curative factor in these cases. With the injection of the serum, however, there was a decided improvement in the patients' general condition and a complete clearing up of the nervous symptoms of encephalitis. Furthermore, we know that the serum protects animals against disease following intracerebral injections of the streptococcus, which is not the case with normal horse serum.

THE PHARMACOLOGY OF MERCURY

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A considerable volume of information has been accumulated on the behavior of mercury in the body. Valuable contributions to the pathologic changes produced in the liver, kidney and other organs have also been made by cases of poisoning in man and by experimental studies on animals. Very few reports, however, have appeared on the pharmacologic action of mercury. Dreser¹ studied the action of various compounds of mercury on the isolated heart. More recently Mueller, Schoeler and Schrauth² reported experiments on the effects of several organic preparations on the circulation and respiration in cats in which injection was made intravenously.

During the past year Kleitman and I carried out experiments with compounds of mercury on different animals and on the isolated heart of the frog and turtle. We have also studied the effect of different substances on the action of mercury, giving some attention to its absorption from the small intestine and when given by intramuscular injection. The results that we obtained showed that small quantities of mercury given intravenously in the form of the succinate, benzoate or acetate produced very severe disturbance of the circulation in all animals, though the effects were not exactly the same in each case. Some differences in reactions were observed in cats, dogs and rabbits. The injection of from 2 to 4 mg. of mercury in divided doses produced a sudden fall of blood pressure, which often occurred after a long latent period (one or two minutes). Blood pressure sometimes fell to zero. The heart stopped at the same time, but arrest of cardiac action was not permanent after doses of 2, 4 or even 6 mg. of mercury. The inhibition of the heart lasted for periods varying from one-half minute to three minutes. Blood pressure then rose suddenly, sometimes reaching a height of 160 mm.

1. Dreser: Arch. f. Exper. Path. u. Pharmacol. **32**: 456, 1893.2. Mueller, Schoeler and Schrauth: Biochem. Ztschr. **33**: 381, 1911.

of mercury, or even more. Since this rise of blood pressure may be ascribed to asphyxia on account of the associated suspended respiration, when the heart stopped, this was controlled by other substances that likewise caused suspension of respiration and arrest of heart action. But no sudden rise of blood pressure occurred on recovery. We performed a number of experiments with acetone in this laboratory, but in no case was the suspension of heart action and respiration followed by an abrupt rise of blood pressure.

This striking resemblance to cardiac inhibition produced by stimulating the vagus nerve suggested the advisability of testing the action of mercury when the vagus mechanism was either partly or entirely eliminated. The administration of the mercury salts after double vagotomy or after paralysis of the vagus endings in the heart by atropin produced exactly the same effects as when the vagus mechanism was intact. As previously mentioned, the response varied in different animals. Dogs were found to be much more sensitive to mercury than cats. Paralysis of the circulation and of respiration occurred in one experiment on a dog after the injection of 2.3 mg. of mercury (as succinate) per kilogram. Nor were the other symptoms of circulatory disturbance and of cardiac irregularity observed in dogs the same as in cats. The reaction of the rabbit to mercury was qualitatively the same as that of dogs, but our experiments indicated that rabbits could tolerate larger amounts of mercury than dogs.

Particularly interesting were the results we obtained in experiments with mercurochrome—220 soluble. This compound is the disodium salt of dibromoxymercury fluorescein, and was first prepared by Young, White and Swartz,³ who reported that it was a substance of very low toxicity. Dogs tolerated 10 mg. of mercury for each kilogram by intravenous injections

piration by intravenous injections given to cats and dogs under urethane and chlorbutanol anesthesia, respectively. The results obtained showed that its action was in some respects decidedly different from that of other organic compounds of mercury, but that it at the same time retained the characteristic effect of mercury. The smallest fatal dose of mercurochrome given intravenously to cats was 14 mg. of mercury for each kilogram. The first indications of circulatory disturbance occurred after 10 mg. of mercury for each kilogram, which is about two or three times the fatal dose of mercury in the form of acetate, succinate or benzoate. Much larger doses of mercury as mercurochrome were tolerated in the other experiments, one of which will be reported for illustration.

A full grown cat under urethane anesthesia received intravenously four injections of 4 gm. of mercury each in twenty-six minutes. There was a slight fall of blood pressure, with cardiac irregularity, which lasted about half a minute. Sixteen minutes later another injection produced a much greater effect, though only half of the preceding amount was used. Heart action was slowed considerably, and blood pressure fell 30 mm. of mercury. The effect lasted only about one minute. During the next forty minutes, 12 mg. of mercury was injected in divided doses. Each injection was followed by cardiac irregularity indicating heart block, but recovery occurred in every case. The administration of the mercury dye was continued. When the total amount injected was 25 mg. of mercury for each kilogram, the blood pressure fell promptly, reaching almost to zero, and heart action ceased. This lasted about one and a half minutes, when blood pressure rose abruptly, attaining almost the same level as before the injection. The pulse was slow at first, but within a few minutes, heart action suddenly became rapid, the acceleration lasting until the next attack. Respiration, which was slowed during the period of cardiac inhibition, stopped when the heart recovered. Though it returned after two minutes, respiration remained permanently slower than before the circulatory changes described set in.

The cardiac effects observed in intact animals were also observed in experiments on the isolated heart of cold blooded animals. The frog heart and the turtle heart were perfused with Ringer's solution containing different amounts of mercury. Tests were made with

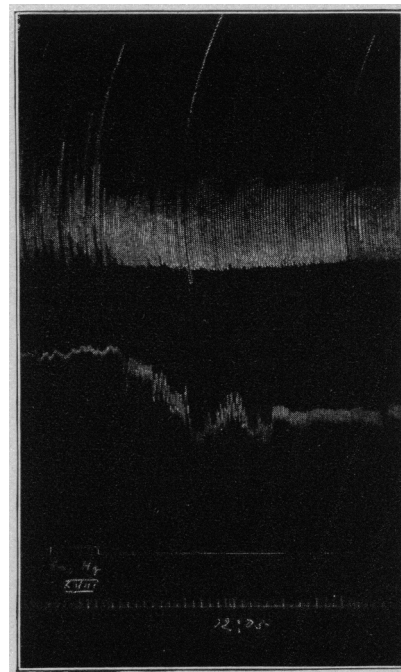


Fig. 2.—A cat, weighing 2 kg., under urethane anesthesia, was given, as Injection 18, mercurochrome-220 soluble. Previously, 42 mg. of mercury had been injected. There was fall of blood pressure; respiration slightly slowed; time, four seconds.

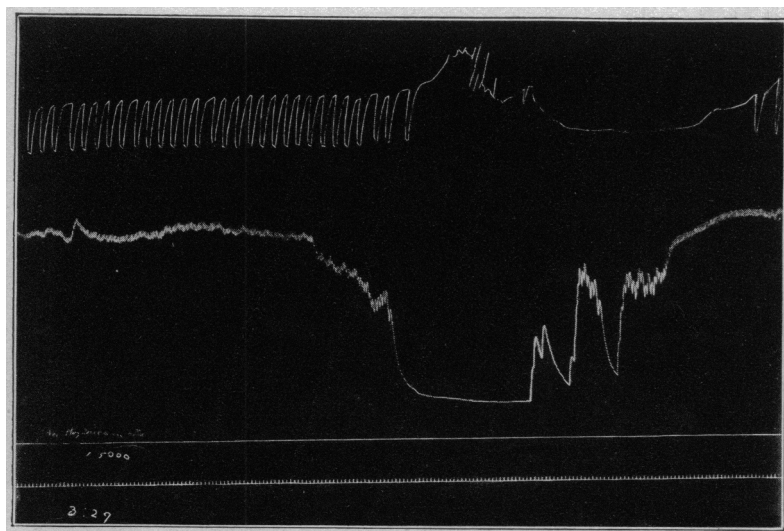


Fig. 1.—A cat, weighing 2.6 kg., under urethane anesthesia, was given 13 c.c. of mercuric succinate (2.6 mg. of mercury) at each of three injections. There was sudden fall of blood pressure after the third injection, arrest of heart action and recovery. Respiration stopped, but also recovered. Upper tracing, respiration; lower tracing, blood pressure; time in seconds.

when it was in the form of mercurochrome, but rabbits were less resistant to this compound. We studied the effects of mercurochrome on the circulation and res-

3. Young, H. H.; White, E. C., and Swartz, E. O.: A New Germicide for Use in the Genito-Urinary Tract. *J. A. M. A.* 73: 1483 (Nov. 15) 1919.

succinate, benzoate and acetate, but we also studied the action of mercuric chlorid. Surprisingly small amounts of these salts proved to be very injurious to the heart. We could reproduce the same phenomena in the heart of the cold blooded animals as we observed in warm blooded animals. Mercury in a concentration of 1:100,000 in Ringer's solution usually produced heart block and delirium cordis in the turtle heart, when perfused for very brief periods. So marked was the toxicity of mercury that delirium cordis sometimes occurred when the turtle heart was perfused with concentrations of mercury of 1:1,000,000 or even 1:10,000,000. The frog heart was more resistant, but the action of mercury also proved to be very powerful on the hearts of these animals. Particularly interesting is the observation we made that the heart may be permanently damaged by mercury, for little or no improvement occurred in the heart of the frog when perfusion with the salts of mercury was discontinued. In the turtle heart some improvement was observed, but complete recovery never occurred after mercury.

Experiments were also made on the influence of mercury on peristalsis. The movements of the intestine in situ as well as the isolated intestine of different animals were studied. Intravenous injections of mercuric compounds failed to produce any effect on peristalsis. The reaction of isolated segments of intestine was not constant. Considerable improvement of the rhythmic contractions, and especially stimulation of tonus, was observed in some experiments. No response or relaxation of the intestine occurred in several others. As these studies are still in progress, no definite conclusions can be drawn at present. It is evident, however, that the reaction of smooth muscle to mercury is quite different from that of the heart.

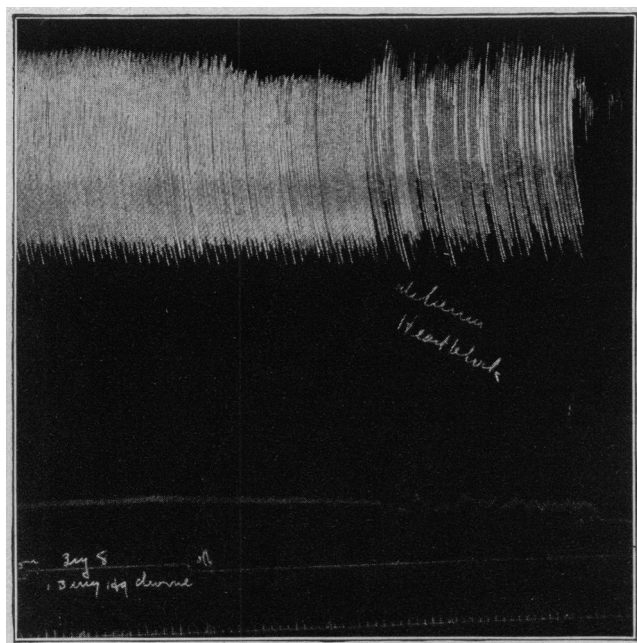


Fig. 3.—A dog, weighing 6.36 kg., under chlorbutanol anesthesia, was given, as Injection 5, 13 mg. of mercurochrome-220 soluble intravenously, which produced heart block, delirium cordis, and finally cardiac paralysis. (Mercurochrome had previously been injected, 8 mg. of mercury for each kilogram). Upper tracing, myocardiogram; lower tracing, blood pressure; time, four seconds.

Cardiac muscle is unquestionably very sensitive to mercury, while the effect of the metal on smooth muscle is at best not considerable. Of interest also

from a practical and clinical standpoint is the absorption of compounds of mercury. Observations were therefore made on absorption when given by intramuscular injection or when solutions of the salts were

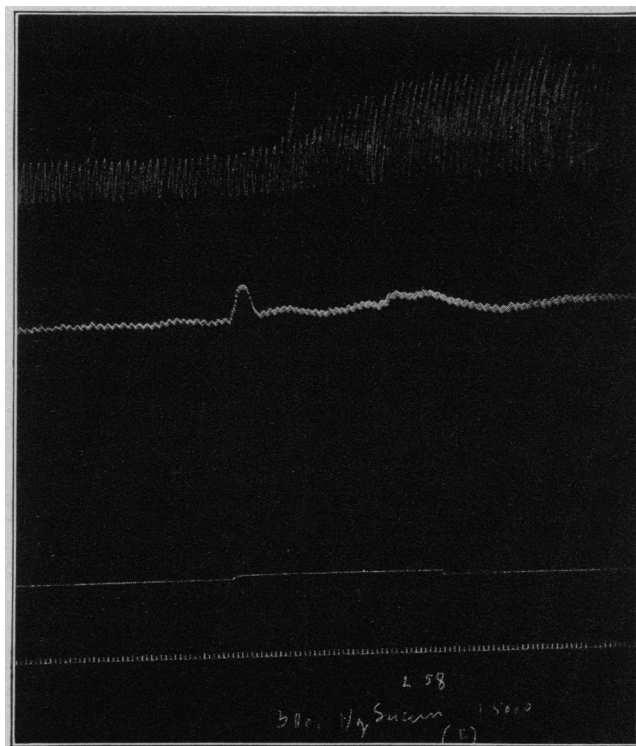


Fig. 4.—A cat, weighing 3 kg., under urethane anesthesia, was injected intravenously with 3 c.c. of 3 per cent. sodium citrate. Ten minutes later, 2 mg. of mercury per kilogram (as succinate), intravenously, stimulated respiration. Upper tracing, respiration; lower tracing, blood pressure; time in seconds.

introduced into the duodenum. When injected into the gluteal muscles there was definite indication that absorption of appreciable amounts occurred within twenty-six minutes. The symptoms produced corresponded to those observed when 4 or 5 mg. of mercury for each kilogram was injected intravenously. Exceptionally, however, the characteristic effects of the metal appeared much later. In one experiment, evidence of absorption was first obtained one hour and forty-five minutes after injection into the muscles.

When mercury was introduced into the small intestine, symptoms appeared much sooner than when given intramuscularly. A fall of blood pressure of 20 mm. of mercury occurred seventeen minutes after the injection of 10 mg. of mercury in the form of the succinate into the small intestine. During the next hour there was a further fall of 70 mm. In another experiment, heart block occurred within ten minutes. As in the case of intramuscular injections, the rate of absorption differed in various animals, the characteristic effects being delayed sometimes about two hours. It may be safely concluded, therefore, that the rate of absorption of organic compounds of mercury from the intestine is fully as good as, if not better than, from the muscles.

Attention may also be called to the observation we made on the effect of various substances on the behavior of mercury in the body. That the action of drugs may be modified by various conditions has often been pointed out by a number of investigators. Indeed, examples of complete reversal of action are by no

means rare. The action of mercury in citrated animals shows that respiration may be considerably stimulated by mercury. When dilute solutions of salts of the metal were injected intravenously into animals after the effect of citrate had worn off, respiration became much more frequent and deeper. The effect in most cases lasted about three minutes, but in one experiment the duration of the effect was about a quarter of an hour. It should be added, in this connection, that the effect of mercury on respiration was independent of the condition of the circulation and that mercury not preceded by citrate never stimulated respiration. However, when considerable amounts of citrate were injected, the subsequent administration of mercury failed to stimulate respiration. Furthermore, we found that large amounts of citrate produced well marked decrease of tolerance to mercury. That mercury may modify reactions to drugs was shown in experiments we carried out with barium and mercury on the isolated heart. We found that when the heart was perfused with barium chlorid in Ringer's solution, after previous treatment with mercury, depression instead of stimulation occurred.

Finally, it may be stated that the action of mercury may be modified also by epinephrin. It was found in several experiments that the onset of delirium cordis and heart block produced by mercury was hastened by the injection of epinephrin.

SUMMARY

In brief, mercury is highly toxic to the heart, causing various cardiac irregularities, such as heart block, delirium cordis and finally paralysis. It is also toxic to the respiration, but the effect in this case is not nearly so pronounced as on the circulation. Furthermore, the action of mercuric salts may be greatly increased by citrate or by epinephrin, suggesting that under certain conditions associated with disturbances of metabolism the toxicity of mercury may be still more increased.

To Remove Rust from Instruments.—First place the instruments in a saturated solution of stannous chlorid, which causes the spots to disappear by reduction. Then rinse the instruments with water and place them in a hot solution of soda soap, and dry. It is also desirable to rub them with a little absolute alcohol and prepared chalk. Another method to remove rust is to place the instruments in kerosene. Paraffin oil is the best preservative against rust, and the most convenient way of applying it without getting an unnecessary thick coating is as follows: One part of the oil is dissolved in 200 parts of benzine, and the objects, after being thoroughly dried and warm, are plunged into the solution. Instruments with joints, as scissors or needle holders, are worked in the fluid, so as to cause it to penetrate into all crevices, and the benzine is then allowed to evaporate in a dry room.—*Pharm. Zentralh.*

INTRAPERITONEAL INSERTION OF BURIED CAPILLARY GLASS TUBES OF RADIUM EMANATION

RESULTS IN TWO CASES OF TUMOR OF THE GASTRO-INTESTINAL TRACT

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The intratumoral application of buried capillary glass tubes containing radium emanation presents a comparatively new departure in radium therapy. The method was originally suggested by Duane, and subsequently developed by the late H. H. Janeway. The

results to date are so gratifying that, in my opinion, the method will play a prominent part in the future development of the whole field of radiotherapeutics.

TECHNIC

Radium emanation—an elementary body in the state of a heavy gas—is the first active product of decomposition of radium. It is collected by means of appropriate apparatus in capillary glass tubes from 3 to 5 mm. long. The tubes, containing between 0.3 and 1.5 millicuries of radium emanation each, are sterilized either by boiling or by immersion in an alcoholic solution of iodine, and are inserted by the aid of a trocar into the tumor tissue. These tubes exert a

comparatively weak but continuous action on the tissues which lasts for several weeks. The cumulative action of 1 millicurie is calculated to equal 132 millicurie hours. Depending on the mass of the tumor, the number of tubes and the strength of each varies. The tumor tissue immediately surrounding the capillary is influenced by the soft beta rays, and may become necrotic. This area of necrosis is minute in extent and acts as a filter on the soft rays. The next zone of tumor tissue is then influenced only by the hard gamma rays of radium. As an ultimate result, the tumor tissue in the vicinity of each capillary tube is replaced by a connective tissue capsule which wholly encloses the tube. The latter meanwhile becomes inert and causes no discomfort to the patient. When the capillaries do not contain more than 1 millicurie of radium emanation and the tubes are not placed too close to one another, there does not take place any sloughing of tissue.

In the course of the last two and a half years, I have used this method extensively on intraperitoneal

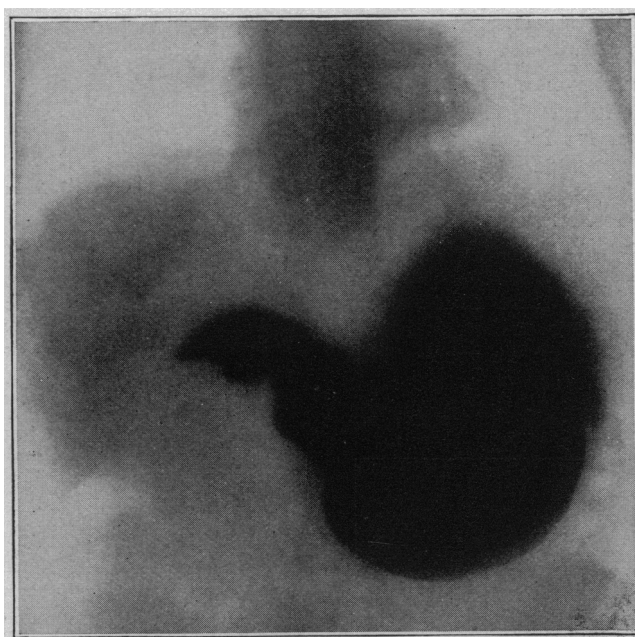


Fig. 1 (Case 1).—Tumor of second part of duodenum before treatment.