

trachea and suprasternal notch, has never caused an increase in scar formation at this point in the line of incision. This has led me to substitute lateral for mid-line drainage in all goiter operations when drainage was deemed necessary. The final results of single and

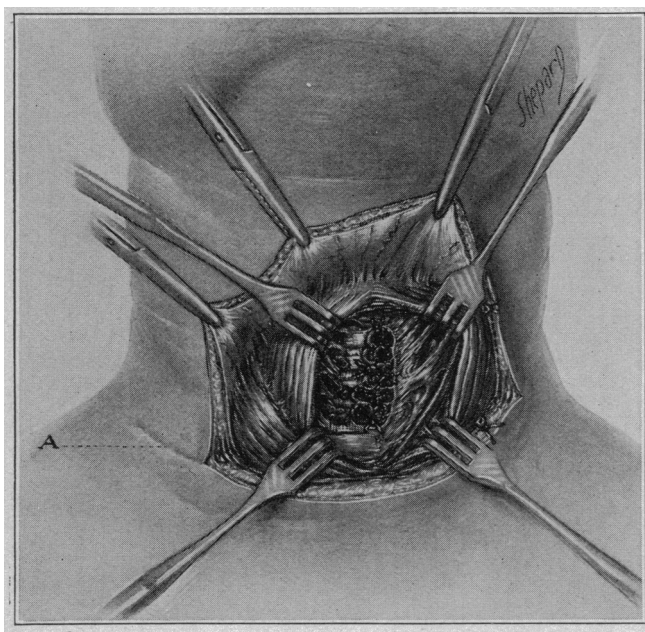


Fig. 5.—The three-quarter incision on the left side. Note the scar, A, from the previous three-quarter incision on the right side.

multiple resections, with lateral drainage, with or without the three-quarter incision, always presented a better looking neck than when the drainage tube was brought out through the suprasternal notch directly over the trachea.

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### THREE CASES OF ACUTE ENCEPHALITIS TREATED WITH SPECIFIC SERUM \*

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AND

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Ever since the pandemic of influenza, an unusually large series of cases of encephalitis has been observed. With each succeeding year the number of cases has gradually decreased; but if our experience is any criterion, there is still an excess of encephalitis over and above that previous to the pandemic.

Our clinical material during the past year has consisted in large measure of the sequels and chronic residues of encephalitis, but we have also observed a number of acute cases, in three of which we used lumbar drainage and the usual symptomatic treatment, with a specific serum recently prepared by one of us (E. C. R.). This serum was obtained from a horse repeatedly injected with a streptococcus isolated from a patient suffering from typical encephalitis.

\* Read before the American Pediatric Society, Washington, D. C., May, 1922.

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### REPORT OF CASES

CASE 1.—B., a girl, aged 5 years, became ill, Dec. 15, 1921. She weighed at birth  $7\frac{3}{4}$  pounds (3.5 kg.); she had been breast fed. At the age of 6 months she had severe pyelitis, with remissions and exacerbations until the tonsils and adenoids were removed in August, 1921.

Physical examination was negative. The child was pale and listless, and did not feel well. December 24, she refused her meals and was very apathetic. The next day her temperature was 100.4; she was nauseated and rather excitable, and slept more than usual. An enema, a cathartic and a mustard bath were given, December 26, but she slept eighteen of the twenty-four hours. The excitability gradually increased until Jan. 1, 1922. She laughed, cried or giggled, and moved around constantly. The leukocyte count was 9,000. January 5, restlessness became very marked, and abdominal pain developed; the leukocyte count was 24,000. Appendicitis was suspected, but no evidence of it found. The leukocytes at two-day intervals numbered 18,000 and 10,000.

January 10, because of extreme irritability, stupor and slight twitching of the extremities, a lumbar puncture was made, and 25 c.c. of fluid obtained under pressure. There were 18 cells to the cubic millimeter; no coagulum formed. The puncture relieved the child's irritability immediately; her mind became clear, and she had better control of muscular movements. January 12, her condition gradually returned to what it had been before puncture, but with more marked choreiform movements. No Kernig or Brudzinski signs were present. The eyegrounds were negative, as were the tuberculin tests.

January 14, a second lumbar puncture was made, and 65 c.c. was obtained under considerable pressure. The fluid contained 50 cells to the cubic millimeter. No tuberculosis bacilli were found. After the withdrawal of fluid there was again a decided improvement, followed by a rapid return of the choreiform movements. When the child was seen, January 17, she was in a state of constant activity, moving

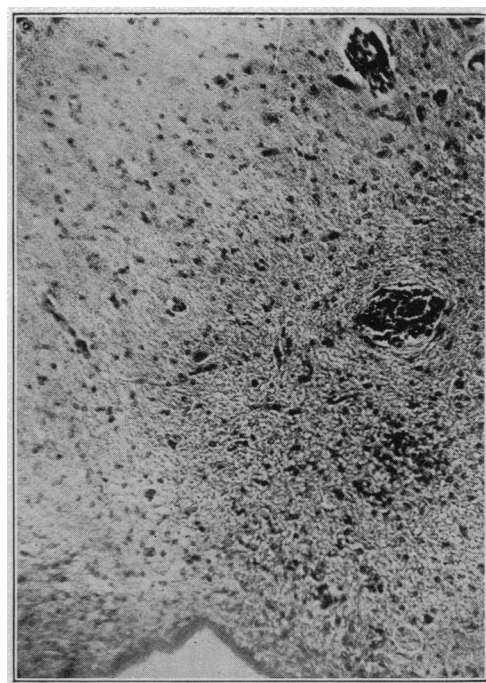


Fig. 1.—Perivascular and localized round-cell infiltration in the pons near the ventricle in rabbit; hematoxylin and eosin,  $\times 1,000$ .

around in her bed and having choreiform movements of her extremities, head, neck and trunk. Her sensorium seemed clear, and physical examination revealed nothing except a slight redness of the nose and throat and a general exaggeration of the reflexes. Swabs were taken from the throat and nasopharynx.

On the afternoon of January 17, after a preliminary desensitization injection of 1 c.c. of serum, 5 c.c. of the encephalitis serum was given. January 18 and 19, 10 and 15 c.c., respectively, were given. After the second injection the child was very much improved, and after the third the nervous manifestations entirely disappeared. The clinical picture of constant motion and choreiform movements completely changed, and she became quiet, lay in her bed, and played with her toys. The choreic movements never returned, and the reflexes became normal. On the third day after the serum was given, the mental and nervous symptoms had all disappeared.

January 24, after two days of increase of temperature (102), the child developed widespread urticaria. After February 12, her temperature became normal. She was up for two hours in the morning and two hours in the afternoon, slept soundly through the night, rested in the afternoon, and seemed perfectly well. April 10, she was still being carefully watched and had had no nervous irritability or choreiform movements. Whether there are any further manifestations must be left to the future.

The swab from the nose was stabbed into plain agar and brought to the laboratory. From this, glucose-brain broth was inoculated and the twenty-four hour culture, which contained a great many colonies of indifferent and green-producing streptococci and a few staphylococci on plating, was injected intracerebrally into rabbits. The organism isolated from the nose was agglutinated by the specific serum. One rabbit received 0.2 c.c., and one 0.1 c.c. of the undiluted culture, one 0.1 c.c. of a 1:10 dilution, and one 0.1 c.c. of a 1:1,000 dilution in salt solution. The first three animals were found dead the following morning. The one receiving the smallest dose had become tremulous and weak in its hind extremities, and had developed marked choreiform movements of the head. These symptoms continued and grew worse until the second day, when the animal died. Marked congestion of the vessels of the pia over the cerebrum, and edema of the pia over the cerebellum were found at necropsy. Cultures from the brain yielded a pure culture of indifferent streptococci; the blood proved sterile. On the basis of the striking train of symptoms noted in this animal, two additional rabbits were injected with 0.1 c.c. of a 1:1,000 dilution of the forty-eight hour glucose-brain-broth culture. They developed almost identical symptoms, as follows:

A rabbit, weighing 1,910 gm., was injected intracerebrally, January 21. January 22 the animal was slightly tremulous, but otherwise well. January 23, respirations were increased, expirations were rapid, almost explosive, and tremor was more marked. The animal was hyperesthetic; it became tremulous and ataxic when hopping, which it was disinclined to do. January 24, the tremor and ataxia were still present, and as the animal hopped it threw its head irregularly. January 25 and 26, the condition remained practically unchanged, and the animal was chloroformed and examined at once. There were no gross lesions in the brain or the cord. The blood was sterile. Culture from the brain on a blood-agar plate yielded a few colonies of indifferent streptococci, and glucose-brain-broth culture yielded a granular growth of the same organism.

Sections of the brain and cord of this rabbit, as of the one injected in the same way which developed identical symptoms, showed moderate mononuclear infiltration of the pia around the blood vessels, rather extensive perivascular round-cell infiltration, which was most marked in the pons (Fig. 1) and upper portion of the medulla, areas of localized infiltration in the brain substance independent of the vessels, and moderate neurophagocytosis in the basal ganglions.

Sections of the brains of the animals that died soon after injection showed moderate infiltration of the meninges, perivascular spaces and adjacent brain substance by leukocytes and round cells in varying proportions, depending on the duration of the experiment.

CASE 2.—F. P., a boy, aged 10 years, had had measles and pertussis, and his tonsils had been removed six months before. His past history was otherwise negative. He had become acutely ill, Jan. 24, 1922, with almost continuous movements of the face and trunk. He lay in a state of semicoma, breathing noisily; his mouth filled with mucus.

Examination revealed weak abdominal muscles, normal reflexes, and pupils reacting to light. His temperature was from 101 to 102. Twenty cubic centimeters of clear spinal fluid was removed; the cell count was 4. January 25, the eyes showed an early choked disk. The child seemed a little brighter for a short time after puncture, but stupor continued. January 27, the temperature was 103.5, and the child was definitely worse. Forty cubic centimeters of spinal fluid was removed, and 15 c.c. of serum was given intravenously. The child was somewhat brighter the next day, and movements had decreased. The temperature remained 103. Eight cubic centimeters of encephalitis serum was given intravenously. January 29, 40 c.c. of spinal fluid was removed. The temperature was 103; the general condition was about the same. January 30, the child seemed definitely brighter and said a few words for the first time. Seventeen cubic centimeters of serum was given intravenously. January 31, the temperature was practically normal. The patient appeared and acted brighter; choreic movements had practically disappeared, and he was resting quietly. Spinal puncture yielded 30 c.c. of fluid containing 14 cells. Twenty cubic centimeters

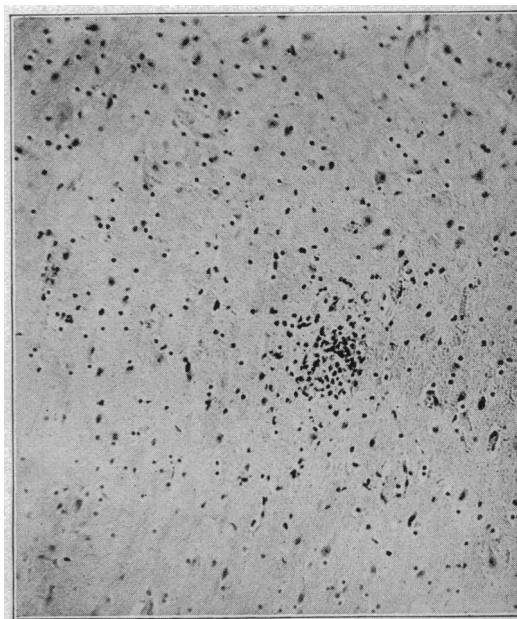


Fig. 2.—Area of leukocytic and round-cell infiltration in the pons of rabbit two days after intracerebral injection with the tonsil strain, after one animal passage; hematoxylin and eosin,  $\times 100$ .

of serum was given. February 1, the general condition was good, and the mind clear. The nervous symptoms had practically disappeared except for occasional grimaces.

February 3, the child's temperature rose to 105; he had a right-sided parotitis, but was otherwise apparently well. February 7, the abscess opened in the right parotid gland. A staphylococcus culture was obtained from the pus. February 12, the temperature remained high. Blood culture yielded staphylococci. The child was very sick; he did not have nervous symptoms, but complained of pain in his legs. February 16, the temperature was normal for the first time.

February 22, the temperature was 102, and pain developed in the arm, knee and toes on the left side. February 24, the temperature was 103. The left ear was discharging, and the left axillary glands were swollen. Blood culture was negative. A rash appeared over the body. March 3, the joints were still painful, and the boy was unable to flex the left foot and toes. An abscess appeared in the left axillary glands. March 7, the temperature was normal, and the foot and toes could be flexed. April 17, the child was in excellent condition, and had gained 10 pounds (4.5 kg.). He limped slightly with his left leg, and the dorsal flexion of the foot was rather weak.

CASE 3.—F. J., a boy, aged 2½ years, was examined in the clinic, March 19, 1922. On the evening of March 17, the

mother had noticed that the child was rather warm and that he slept restlessly. The next morning he developed general convulsions that recurred at irregular intervals of about one hour. He was semicomatose most of the day, and when seen by the local physician in the evening, he could be aroused only with difficulty; his temperature was 102.6 by axilla. March 19 he had convulsions, recurring at irregular intervals, and could no longer be aroused from his coma. The convulsions were more marked in the right side.

During his examination in the afternoon of March 19, he lay in deep coma. He had a slight stiffness of the neck, his nose and throat were slightly red, and his tonsils were swollen but without exudate. The findings in the chest and abdomen were negative. The Babinski, Brudzinski and Kernig signs were negative.

A lumbar puncture yielded 25 c.c. of clear fluid under increased pressure. The Nonne test was negative. The cell count was 80 questionable (because of acid). The following morning only one cell was found. No change in his condition followed the puncture. He entered the hospital at 10 p. m., March 19. His temperature was 105, pulse 140, and respiration 34. The erythrocytes numbered 3,420,000; the leukocytes, 5,000; the hemoglobin was 67 per cent.; the polymorphonuclears, 67 per cent.; lymphocytes, 38 per cent., and large mononuclears, 6 per cent. A trace of albumin was found in the urine. Convulsions continued during the night. Chloral given at 3 a. m., March 20, controlled the convulsions, but they recurred at 9 a. m. At 10 a. m., 10 c.c. of serum was given intramuscularly. Swabs were taken from the nose and throat. The child seemed drowsy, and slept most of the day. He was rather restless during the night, but convulsions did not return.

March 21, 15 c.c. of serum was given, and lumbar puncture repeated; there were 11 lymphocytes to 1 cubic millimeter. The Nonne test was negative. Culture revealed a green-producing streptococcus. The patient appeared much better, talked intelligently, and asked for food. A divergent squint (present since birth) was very evident. March 22, the temperature was 104, the pulse 130, and the respiration 32. March 25, the child's temperature was normal for the first time, and he seemed entirely recovered. April 10, the home physician reported a single convulsion without fever or other symptoms, but no recurrence since then.

#### EXPERIMENTS ON ANIMALS WITH THE ORGANISMS ISOLATED FROM THE TONSILS AND THE SPINAL FLUID

A small amount of pus was expressed from the tonsils, and suspended in 2 c.c. of salt solution. Two rabbits were injected intracerebrally, one with 0.2 c.c. of the suspension, and the other with 0.2 c.c. of a 1:100 dilution.

The first rabbit was found dead the next morning; the vessels of the meninges were markedly congested, and there was a hemorrhage at the point of injection in the right frontal lobe.

The second rabbit, weighing 1,170 gm., was injected intracerebrally, March 20, with 0.2 c.c. of a 1:100 dilution of the salt solution suspension of the pus from the tonsils. March 21, at 7 a. m., the animal appeared well. At 2 p. m., its respirations were somewhat increased and it was decidedly tremulous. At 2:30 p. m., it developed peculiar attacks of tonic spasms of the muscles of the fore extremities, head and neck, in which it usually turned its head rather sharply to

the right, and sometimes sharply downward. The attacks recurred at intervals of from two to five minutes. In some of the more severe attacks the animal extended its fore extremities in a stiff manner, raising the forepart of its body almost to the point of falling over backward, and holding its head rigid. It drooled saliva. At 2:45 p. m., the tonic spasms of the muscles of the forepart of the body continued. Between attacks the animal appeared half asleep, and rested its head on the floor. At 2:50 p. m., during an attack, it suddenly plunged forward for a short distance, fell to its side, kicked violently with fore and hind extremities, urinated, held its breath, and seemed to be dying. Respirations then returned slowly, and it lay quietly on its side. Repeated tonic contractions of the right fore and hind extremities, head and neck followed. At 3:10 p. m., it had another convulsive attack. From 3:15 to 3:25, the attacks recurred frequently; in the intervals, the animal was semicomatose, and at the end of each attack it turned its right eye sharply forward and inward, holding its head very stiff. At 3:30 the attacks continued, but were less severe. The animal was growing weaker, and the respirations were feeble. At 3:40 p. m., it died without a struggle. The animal was examined at once.

The vessels of the meninges were extremely congested, but there were no hemorrhages in the brain or the cord; the cerebrospinal fluid was slightly turbid; the stomach was tightly contracted over a large amount of contents, and the mucous membrane contained numerous linear hemorrhages. There was no mark at the point of inoculation. Cultures from the blood and the brain yielded a large number of green-producing streptococci.

A mixture of equal parts of the primary (twenty-four hour) and secondary (ten hour) cultures of the suspension of pus from the tonsils was injected intracerebrally into two rabbits, one receiving 0.1 c.c., the other 0.2 c.c., of a 1:1,000 dilution of the neutralized culture.

The first rabbit was extremely shaky and tremulous, and had several attacks of slight but universal spasms. It was found dead the second day.

The second rabbit, weighing 1,610 gm., was injected intracerebrally, March 21, 1922, with 0.2 c.c. of a 1:1,000 dilution of equal parts of primary and secondary glucose-brain-broth culture from the tonsils. March 22, the animal sat quietly, rather humped up, and was disinclined to hop. It was slightly hyperesthetic, and the respirations were slightly increased. At noon the next day it had repeated spells of quivering of the muscles of the neck on the left side, hopped slowly, and was a bit shaky. At 7:30 a. m., March 24, the animal was found sitting in a corner of the cage having repeated spells of clonic spasms of the muscles of the left side of the neck and the left shoulder. At 8:30 a. m., the attacks had grown worse; the spasms of the muscles had become continuous; the head was held downward and to the left; the muscles of the fore extremities twitched repeatedly, as the body was raised high. At 9 p. m., the spasms of the muscles of the forepart of the body still continued. When the animal was prodded, general tonic spasms of the muscles developed, first on the left side and then on both sides. In one of these the animal fell on its side, relaxed, gasped for breath, had a recurrence of the spasms involving the muscles of almost the entire body, more marked on the left side, and died, apparently from cardiac failure. It was examined at once.

The vessels of the meninges were markedly congested, but there were no hemorrhages in the brain or the cord, and

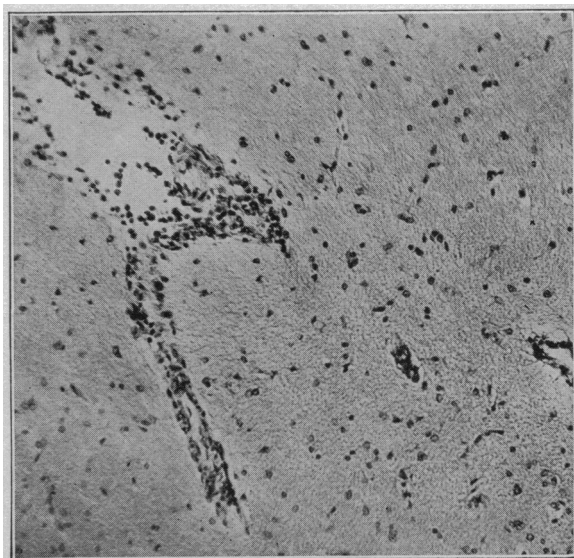


Fig. 3.—Leukocytic and round-cell infiltration of the pia and around blood vessels in the brain of rabbit five days after intracerebral injection with the strain from the spinal fluid; hematoxylin and eosin,  $\times 100$ .

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. Dreser<sup>1</sup> studied the action of various compounds of mercury on the isolated heart. More recently Mueller, Schoeler and Schrauth<sup>2</sup> 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.