A few years ago the attention of one of the writers was called to a case in which ill effects appeared to have resulted from the use of thallium acetate as a medicinal agent in the treatment of persistent night sweats. A careful review of the available literature at that time revealed very few papers dealing with the physiological action of thallium, yet these recorded many interesting, though often conflicting, statements and thus became the incentive to the following study.

In a brief summary of the literature of the subject, mention should first be made of the work of Lamy, who discovered thallium and independently identified it as a new element only a short time after Crookes had found it. He was afflicted with general lassitude and a weakness of the lower limbs while engaged in an extensive study of the chemical properties of the element. Suspecting thallium as the cause he was the first to test its toxicity by dissolving five grams of thallous sulphate in milk and offering it to two young pups. These refused the milk after drinking a little of it, but by inadvertence six ducks, two hens, and a dog were allowed to partake of the remainder. Some hours later the dog became ill, was restless and refused food. During the night symptoms of distress became more prominent, the back was arched, respiration was labored and salivation was noted. The hind limbs, at first convulsive in movement, became partially paralyzed and this general condition was maintained until complete prostration and death occurred 64 hours after the fatal effects appeared to have resulted from the use of thallium acetate as a medicinal agent in the treatment of persistent night sweats. A careful review of the available literature at that time revealed very few papers dealing with the physiological action of thallium, yet these recorded many interesting, though often conflicting, statements and thus became the incentive to the following study.

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Toxicity of Thallium Salts

meal. On the evening of the dog's death the hens and ducks were found dead, or dying, a paralysis of the legs being a general symptom among those yet living. Finally both pups died in spite of every effort to save them. The symptoms emphasized by Lamy were weakness, abdominal pain, trembling, more or less effective paralysis of the hind legs, constipation, loss of appetite, and difficulty in breathing.

In the same year Paulet expressed the opinion that thallium is a more energetic poison than lead. Grandeau, noting the similarity in the symptoms of lead and thallium poisoning, made a few tests of their relative toxicity. A gram of thallous sulphate administered to a dog caused death in five days with all the symptoms of lead poisoning. One and one-half gram of lead acetate caused vomiting but in a few days the dog appeared to be normal. Soon after the publication of Lamy's observations on the toxic action of thallium, Crookes expressed his doubt of its being extremely poisonous, since he had experienced no inconvenience from breathing its vapors or from taking doses of one or two grains (.0648 to .1296 gram) of its salts. The sulphate colors the nails and hair as do the salts of mercury and causes the skin to become yellow and horny.

Marme observed a tolerance for small amounts of the poison but claimed that the effects are cumulative. Blake studied the effects of thallous preparations when injected intravenously. He injected .090 gram of the sulphate into the jugular vein of a rabbit. Blood ceased to flow into the lungs, owing, he asserts, to the pulmonary ganglions being affected, but after some seconds the circulation was restored and no further abnormal symptoms appeared. A second dose caused death. No results were observed after the injection into the carotid artery of various amounts up to .350 gram, but .750 gram caused death from

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3 Crookes: Chemical News, viii, p. 159, 1863.
4 Through a typographical error in the Jahresb. d. Chem., p. 256, 1863, the amount of thallium salts which Crookes is said to have taken with impunity is given as one or two grams.
5 Marme: Journ. d. pharm., 4e serie, x, p. 263, 1867.
6 Comp. rend., iii, p. 57, 1890.
"stoppage of pulmonary circulation." Luck\textsuperscript{1} is reported to have conducted a series of experiments on warm blooded animals but the writers have been unable to secure a copy of the original paper or a satisfactory abstract of it. Curci\textsuperscript{2} observed that thallium depressed the heart and circulation in frogs. General weakness, decreased sensibility, and difficulty in breathing preceded death which was ascribed to heart failure. In warm blooded animals he noted general weakness, collapse, and coma preceding death. In dogs the pulse was slower after the poison was given, although the blood pressure rose. After a dose of curare large enough to affect the heart and vasomotor centers, thallium caused a rise of pressure. A close resemblance to the alkali metals in physiological action is claimed for thallium by this author.

Thallium appears to have entered materia medica on the recommendation of Combemale\textsuperscript{3} who cites the acetate as an effective remedy for night sweats. It was to be taken daily for not more than four days in succession in the form of a pill containing .100 gram of the salt. Not long afterward there appeared almost simultaneously two papers noting instances in which more or less serious after effects followed this treatment. Dubreuille\textsuperscript{4} observed in one patient, a notable case of alopecia with its characteristic loss of hair. A similar action was reported at some length by Jeanselme\textsuperscript{5}. A woman had been troubled by severe night sweats for several years. Thallous acetate was prescribed, and the patient received in three days nine pills, each containing .030 gram of thallium acetate, a total of .270 gram. The treatment was then discontinued not only because the perspiration became less profuse but also because the patient suffered severe pains in the abdomen and legs. In the course of a fortnight the hair of the head, eyebrows, and eyelashes began to fall out in large quantities although the patient was otherwise well except for a mild digestive disorder. A month later the hair was growing better, but some of the hairs were found to be con-

\textsuperscript{1} Luck: *Dissert. Dorpat.*, 1891.
\textsuperscript{2} Curci: *Ann. chim et pharm.*, xii, p. 181.
\textsuperscript{3} U. S. Dispensatory, 18th ed.
\textsuperscript{4} Dubreuille: *Soc. de l'anat. et de physiol. de Bordeaux*, 1898.
\textsuperscript{5} Jeanselme: *Bull. soc. franc. de derm. et syph.*, p. 374, 1898.
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stricted and discolored for a short distance above the scalp. There was no recovery of the hair which had fallen out and apparently many of the hair follicles had been irremediably injured. An examination of some of the hair by decomposing it with concentrated nitric acid, subjecting the resulting concentrated and neutralized solution to electrolysis, and testing the deposit spectroscopically for thallium, yielded negative results. Hallopeau,¹ thinking that thallium might be used to remove superfluous hair, rubbed a salve containing thallium acetate into the skin of a guinea pig. The treatment killed the subject but the hair on the rubbed surface was unchanged. It has been claimed² that injections of thallium are followed by general muscular atrophy, especially marked in the jaw and spine; also that it exerts a powerful depressant action on the heart, while baldness is induced in man.

Of late years no attention seems to have been devoted to this subject.

EXPERIMENTAL DATA.

Thallous salts prepared from metallic thallium and carefully freed from the less stable corresponding thallic compounds, were employed exclusively in this investigation. The acetate, sulphate and nitrate are all crystalline, stable in air, and freely soluble in water. In every case where the dose is recorded it is expressed as metallic thallium, calculated from the known light of the salt used. The general course of the more important experiments is outlined in the following protocols.

I. A large white rat received subcutaneously 10 mg. of thallium as the nitrate at 10:15 a.m. The following day a notable lack of coordination in movement was observed and food was refused. Another injection of 10 mg. was given at 4:15 p.m. Soon thereafter the rat rapidly became stupid and moped in a corner. Nervous tremors began to appear, growing in frequency. Gradually the animal passed into a comatose condition, showing frequent micturition, thus passed the third day, and died during the night.

II. A second white rat was injected subcutaneously with 20 mg. of thallium at 11:30 a.m. It became stupid in a few hours; recovered position with difficulty when placed on its back; very little food taken;

¹ Hallopeau: Bull. soc. franc. de derm. et syph., p. 374, 1898.
² Richet: Quoted by Cushny: Pharmacology and Therapeutics, p. 707.
increased excretion of urine marked; nervous tremors. On the following
day a second injection of 25 mg. was given, after which the animal sank
rapidly and died during the night.

III. A guinea pig received subcutaneously 5 mg. of thallium as the
sulphate. Dose repeated on each of the following two days. No change
apparent until the third day when lack of coördination was observed in
the awkward use of the hind limbs. On the fourth the appetite failed,
on the fifth the head began to tremble and lack of coördination was marked.
Death followed during the night of the sixth day.

IV. Another guinea pig treated in exactly the same manner displayed
the same symptoms in the same order, death resulting as before on the
sixth day.

V. A rabbit was given subcutaneously 20 mg. of thallium as the ace-
tate. There was no apparent change beyond loss of appetite and little
disposition to move about, so another injection of 20 mg. was given on the
second day. Third day: Subject stupid and showed evident weakness
in hind limbs. Food was refused, the trembling of the head began to
appear, and on the evening of the fourth day death ensued. Upon autopsy
the lungs presented the usual appearance following death by asphyxia
and the intestinal walls were slightly inflamed; the bladder was distended
with urine, which gave a strong test for albumin and showed thallium
weakly with the spectroscope.

VI. A second rabbit received by subcutaneous injection a dose of
10 mg. of thallium as the acetate. No change was observed and on the
next day another injection of 10 mg. was given. Again no change until
the third day when he mooped somewhat but ate a little. The head began
the characteristic trembling late in the afternoon. On the fourth day
food was refused, a semi-conscious condition supervened and death resulted
in the evening.

VII. Another rabbit was given 5 mg. of thallium subcutaneously
daily four times in succession. No change was noted until the last day of
injection when the familiar moping began, accompanied by loss of appetite
and lack of coördination in the hind limbs. On the fifth day food was
refused; on the sixth general weakness and a trembling of the head were
prominent; and early on the seventh day death occurred.

VIII. A rabbit which had been used as one of several controls was
given 5 mg. of thallium as acetate subcutaneously. The animal ate well
and was lively until the fifth day when he appeared sluggish. The follow-
ing two days noted a steady decline and a refusal of all food, death result-
ing on the eighth day, with the usual symptoms which had been observed
with approaching death in other cases.

IX–X. This result was so surprising that two other rabbits were
injected similarly with 5 mg. of the salt. No symptoms of thallium
poisoning were noted after nine days of observation and the animals were
released.

XI. This subject was a healthy mongrel dog—weight about 22 kg.
One gram of thallium as the nitrate was administered subcutaneously at
Towards evening he became restless and the following morning was very sick; the hind limbs were partially paralyzed and the eyes were lusterless. As the day advanced a disturbance of respiration was plainly evident in spasmodic and labored breathing—a condition which continued until the end. Vomiting occurred late on the second day. Marked weakness, a striking lack of coordination in the hind limbs, a refusal of food and nervous tremors were features of the third day. The eyes were badly affected, much wax and mucus collecting behind the lids. Tears were seen constantly. The urine was increased notably in volume. The animal gave very little expression of pain, seeming on the contrary to be less sensitive to all stimuli. On the fourth day there was great weakness, low temperature and convulsive breathing. Death occurred during the night, about eighty hours after the dose was administered. No prominent lesions were noted on autopsy. The urine in the bladder gave a considerable precipitate of albumin, and from it also a small quantity of thallium sulphide was precipitated. Thallium was found also in the waxy secretions of the eye.

XII. A healthy Newfoundland dog, weighing 27 kg. was given .5 gram of thallium as the acetate per os with meat at 10 a.m. At 5 p.m. a slight weakness was noted in the hind limbs. On the second day there was very apparent loss of control of the hind limbs, which moved in a "jerky" manner when the dog walked. No albumin but a trace of thallium in the urine. Third day: Food was taken; feces, slightly colored with blood, and urine were passed with difficulty; albumin in urine; marked aphrodisiacal action. Fourth day: Hind limbs weak and partially paralyzed, playing the dog queer tricks in locomotion; urine in large quantity passed with difficulty, the animal being unable to assume his usual position in performing this function, sprawled awkwardly; appetite poor; pronounced test for albumin and slight test for thallium in urine. Fifth day: All food refused; nervous twitchings began; small amount of yellow liquid vomited. Sixth day: Food refused; conjunctivitis and dilation of pupils noted. Seventh day: Hind limbs nearly useless; respiration became labored; urine scanty. Eighth day: Little change, but visibly weaker; aphrodisiosis continued. Ninth day: Subject very weak; urinated with difficulty and passed with much straining a small amount of feces; unconscious at 2 p.m.; spasmodic breathing gradually becoming slower until 3:30 p.m. when death ensued.

XIII. A young bitch weighing about 9 kg. was caged and fed on a mixed diet of meat and cracker meal. She was placed under light ether anesthesia and injected subcutaneously with 50 mg. of thallium as the acetate, at 4 p.m. The next day a lack of coordination was plainly apparent in the hind limbs. At 3:30 p.m. another injection of 50 mg. was given. Third day, lack of coordination was striking at 9 a.m. When the subject was released to run about the room the hind legs would give way suddenly and sprawl awkwardly with every change of direction. Whole posterior region seemed greatly weakened. The dog stood with knees flexed. Appetite good. Fourth to ninth days: Same general condition main-
Robert E. Swain and W. G. Bateman

tained; food relished; urine increased notably in volume. Toward the end of this period, the subject became less lively and was often found lying on the back with feet in air. With the dog standing a slight pressure with the hand in the lumbar region would cause the hind legs to give way at once. Tenth day: Appetite impaired and eyes affected. During the following three days all food was refused, diarrhea was persistent, and a condition of general weakness developed. The hair and even the skin was eroded from the face in the path of the lachrymal secretions. Altogether a sorry looking subject. Fourteenth day: A little food taken; diarrhea improved, general condition better. Thence until the eighteenth day a gradual improvement was maintained, but the hind limbs were yet weak. Finally the animal became cheerful and normally hungry again and was released to trampdom as a reward for having recovered from such a serious condition. This recovery was a surprise of the course of experiments. The samples of urine collected gave pronounced tests for albumin and good tests for thallium until the animal was well along toward recovery.

Effect of repeated small doses per os. XIV. A healthy young dog was given 15 mg. of thallium as the acetate daily for thirteen days, a total of 195 mg. The hind limbs were first affected on the third day, a condition which thenceforth became rapidly more severe. The appetite weakened on the seventh day and failed entirely on the twelfth. Occasional vomiting and diarrhea appeared near the close of the dosing period. On the last day of the dosing period (thirteenth) there was great weakness and emaciation, the abdominal region was greatly constricted and the back bent. The dog was on his feet only once during the day and then got up to evacuate when an intestinal hemorrhage followed. The first signs of a disturbed respiration appeared toward evening. On the fourteenth day respiration was very irregular and labored, the animal sank into partial unconsciousness and died early on the fifteenth day. On post-mortem examination the subject was found to be greatly emaciated. Small ulcerous sores were noted on the inside of the thighs of the hind legs and on the abdomen. The gums were discolored by a purplish blue line at the base of the teeth. The gall bladder was distended with bile. The intestines were intensely congested throughout their entire length. Free blood was found in the small intestine, the whole inner wall of which was extensively inflamed. The urine began to yield tests for albumin early in the dosing period, the amount increasing as the case progressed. Tests for sugar, bile, and blood were negative. In a few samples casts of the hyaline type were observed.

XV. The subject of this test was an active and healthy dog of about 21 kg. weight. He was fed on lean meat and cracker meal for several days and then given 40 mg. of thallium as the nitrate on each of five successive days. In this case the same symptoms were manifested as in the other cases and developed in the same order,—lack of coordination in hind limbs, diuresis, loss of appetite, nervous tremors, albuminuria, vomiting, diarrhea, aphrodisiosis, respiratory disturbance and death on the fifteenth day. Post-mortem examination revealed ulcerous sores and pus sacs in
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de the pelvic region, the common purplish blue line around the gums, a
gall bladder greatly distended and filled with bile and the unfa
inflammatory condition of the intestines. Albuminuria first appeared faintly
on the fourth day and increased in severity until the twelfth when very
large amounts of albumin were found in the urine.

The table on following page gives an outline of the experi-
ments on warm blooded animals.

Experiments on cold blooded animals. A number of toads were
injected with thallium acetate in single and repeated doses vary-
ing from .001 gram to .030 gram. Injections were made directly
into a lymph sinus on the back, and as in the other experiments
proper controls were kept under observation during the course
of the tests. The results indicate that doses of .005 gram and
upward are fatal to these animals, which average about 300 grams
in weight. Even this usually lethargic organism, however, mani-
fested in a very decisive way the main symptoms which marked
the course of action in mammals. Loss of control of the hind
limbs and death by asphyxia were always prominent, the nervous
mechanism controlling the heartbeat seeming to be unaffected
while that of respiration was influenced to such an extent that
this became the immediate cause of death.

Two rectangular glass battery jars having a capacity of about
thirteen liters were filled with fresh sea water, the bottom covered
with sand and stones, and sea lettuce added to assist in keeping
the water properly oxygenated. Thallous chloride to the
amount of .6104 gram was dissolved in the water of one of the
tanks, thus providing a 1:2500 thallium solution. A toad fish
was placed in each tank. These fish (genus Porichthys), weigh-
ing 30 to 50 grams, are very hardy, being accustomed to with-
stand lack of food and great changes in the concentration of the
sea water in which they thrive as a result of frequent isolation
in pools between high tides. Within a few hours the respiration
of the test fish became labored and spasmodic. Early on the
second day its movements were sluggish and dyspnoea was
marked, but as the day advanced the subject showed signs of
great distress. The head was thrown violently upward and
the gills worked painfully. Swimming movements were erratic
and weak and the fish drifted helplessly into collision with the
stones or the sides of the vessel. At noon it turned on its side
<table>
<thead>
<tr>
<th>NO.</th>
<th>DATE</th>
<th>SUBJECT</th>
<th>SALT USED</th>
<th>ADMINISTERED</th>
<th>DOSAGE</th>
<th>DAYS GIVEN</th>
<th>TOTAL</th>
<th>OBSERVATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Jan. 29, '08</td>
<td>White rat</td>
<td>nitrate</td>
<td>subcutaneously</td>
<td>0.010</td>
<td>2</td>
<td>0.020</td>
<td>Died on second day</td>
</tr>
<tr>
<td>II.</td>
<td>&quot; 30, '08</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
<td>0.020</td>
<td>2</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Feb. 4, '08</td>
<td>Guinea pig.</td>
<td>sulphate</td>
<td></td>
<td>0.005</td>
<td>3</td>
<td>0.015</td>
<td>Fifth `</td>
</tr>
<tr>
<td>IV.</td>
<td>&quot; 4, '08</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
<td>0.005</td>
<td>3</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>V.</td>
<td>June 4, '08</td>
<td>Rabbit</td>
<td>acetate</td>
<td></td>
<td>0.020</td>
<td>2</td>
<td>0.040</td>
<td>Fourth `</td>
</tr>
<tr>
<td>VI.</td>
<td>&quot; 4, '08</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
<td>0.010</td>
<td>2</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>&quot; 8, '08</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
<td>0.005</td>
<td>1</td>
<td>0.005</td>
<td>Seventh day `</td>
</tr>
<tr>
<td>VIII</td>
<td>&quot; 14, '08</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
<td>0.005</td>
<td>1</td>
<td>0.005</td>
<td>No serious effects; recovered</td>
</tr>
<tr>
<td>IX.</td>
<td>&quot; 14, '08</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
<td>0.005</td>
<td>1</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>X.</td>
<td>May 28, '08</td>
<td>Dog (wt. 22 kg.)</td>
<td>nitrate</td>
<td>per os</td>
<td>1.000</td>
<td>1</td>
<td>1.000</td>
<td>Died on fourth day</td>
</tr>
<tr>
<td>XI.</td>
<td>June 3, '08</td>
<td>&quot; 27</td>
<td>acetate</td>
<td></td>
<td>0.500</td>
<td>1</td>
<td>0.500</td>
<td>Ninth `</td>
</tr>
<tr>
<td>XII.</td>
<td>Oct. 26, '08</td>
<td>&quot; 9</td>
<td>&quot;</td>
<td>subcutaneously</td>
<td>0.050</td>
<td>2</td>
<td>0.100</td>
<td>Seriously affected but recovered.</td>
</tr>
<tr>
<td>XIII</td>
<td>Jan. 1, '09</td>
<td>&quot; 10</td>
<td>&quot;</td>
<td>per os</td>
<td>0.015</td>
<td>13</td>
<td>0.195</td>
<td>Died on fifteenth day</td>
</tr>
<tr>
<td>XIV.</td>
<td>&quot; 13, '09</td>
<td>&quot; 12</td>
<td>nitrate</td>
<td></td>
<td>0.040</td>
<td>5</td>
<td>0.200</td>
<td></td>
</tr>
<tr>
<td>XV.</td>
<td>Oct. 3, '08</td>
<td>&quot; 9\frac{1}{2}</td>
<td>sulphate</td>
<td></td>
<td>0.050</td>
<td>5</td>
<td>0.250</td>
<td>Twelfth `</td>
</tr>
<tr>
<td>XVI.</td>
<td>&quot; 31, '08</td>
<td>&quot; 9\frac{1}{2}</td>
<td>acetate</td>
<td></td>
<td>0.030</td>
<td>4</td>
<td>0.120</td>
<td>Eighth `</td>
</tr>
<tr>
<td>XVII</td>
<td>&quot; 31, '08</td>
<td>&quot; 15</td>
<td>nitrate</td>
<td></td>
<td>0.100</td>
<td>3</td>
<td>0.300</td>
<td>Seventh `</td>
</tr>
</tbody>
</table>
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and soon thereafter made a quick rush to the surface, making desperate efforts to breathe, and then fell head downward to the bottom where death occurred an hour later, and fifty hours after the beginning of the experiment. That lack of oxygen in the water was not even a contributing cause of death was shown by the normal respiration and activity of the control.

This experiment was repeated, using a toad fish and a young rock cod (genus Cottidae). The rock cod died during the following night after displaying signs of embarrassed respiration within a few hours after being placed in the tank. The toad fish was seriously affected at the close of the second day and though transferred to fresh sea water, the symptoms progressed unabated, death occurring 53 hours after the test began. In other experiments at a concentration of 1:250 death resulted within 20 hours.

In order to test the resistance of fish of larger variety toward thallium salts injected into the body, a large concrete tank was filled with fresh sea water and in it were placed three bull fish (genus Sebastodes) and two "blue cod" (Ophidon elongatus). Seaweed, rocks and sand were added and a stream of fresh sea water was kept running through the tank much of the time. Mussels, which were eaten greedily, were provided as food. After being two days under observation, three of the fish were injected with thallium acetate directly into the lymphatic trunk just behind the lateral fin.

No. II. Blue cod, weight 750 grams (approx.). Given 15 mg. thallium.
No. III. Bull fish, weight 1900 grams. Given 15 mg. thallium.

Second day: No I appeared to be normal. No. II was affected, being sluggish in movement. No. III was normal, and received another injection of 15 mg. Third day: No. I was less active and appeared ill. No. II was in a dying condition at 10 a.m., with the gill movements irregular and convulsive. Death followed at 2 p.m. No. III was seriously affected and gave scarcely any response when disturbed. It showed a tendency to lie on one side and swim in a circuitous path. Fourth day: No. I was visibly affected. There was a notable loss of control of direction in swimming. The fish swam repeatedly head forward against the side of the tank when trying apparently to avoid it. Ex-
haustion came on quickly after slight exertion. The body was tilted to one side in swimming and resting. No. III died at 9 a.m. Fifth day: No. I was found dead at 8 a.m. The controls were normal and active.

Discussion of results. It would appear from these experiments that thallium deserves to be classed among the most toxic of the elements, progressing in its physiological action with a remarkable certainty and definiteness. In general death has been found to result from smaller doses than any yet emphasized by previous investigators. Lamy expressed great surprise that five grams of thallous sulphate (containing 4.06 grams thallium) should kill a dog, two young pups, six ducks and two hens. In these experiments two rats, two guinea pigs, four rabbits, six toads, and seven dogs have been killed with less than 3 grams of thallium.

It is apparent that thallium stands in an entirely different class from lead, which it greatly excels in toxicity, and ranks very close to arsenic. That the latter is the more deadly however when administered in a single dose, is hardly to be doubted. Accepting .200 gram of arsenious oxide as a fatal dose for an adult, it seems highly improbable that that amount of thallium in a single dose would cause death in man, although it might be expected to give rise to a serious disturbance of the appetite and digestion, and of the power of coördinated movement in the lower limbs. One important difference in comparison with arsenic may be emphasized here and that is the absence of any apparent tolerance for the metal. The administration of a given amount of one of its salts in repeated small daily doses seems to be scarcely less effective than when given as a single dose. This tendency toward a strong cumulative action is indicated in a number of the experiments, notably Experiment XIV where .195 gram, given in thirteen daily doses of .015 gram each, produced death in the same time as .200 gram given in five doses of .040 gram each.

The symptoms displayed by all the subjects have shown a striking and consistent conformity and have developed in well defined order. The first one to appear is that of lack of coördination in locomotion, and this is shown by dogs, rabbits, toads and fishes alike. In quadrupeds this difficulty is localized in the
hind quarters, which gradually become more or less completely paralyzed. With fishes there is lack of balance, the subject swims in queer positions and is unable to guide or steer himself in the desired direction. This symptom develops very soon after the poison is given and very small amounts are enough to cause its appearance. After injection with 50 mg. one dog (XIII) displayed it 15 hours later, and another (XIV) made vague and awkward motions with his hind legs after 45 mg, had been given in three daily doses of 15 mg. each.

Among the nervous disorders a persistent trembling of the head has been noticed in all warm-blooded subjects. In some cases great dilation of the pupils was observed and general tremors all over the body were common. At times the dog shivered as though cold. The skin was always dry.

The urine is greatly increased in quantity for some days after thallium is first administered. In one dog (XVI) the average daily amount of urine before dosing was 450 cc., during the dosing period, 600 cc., and after this irregular in quantity and often lacking altogether on certain days. In another case (XVII) the normal average daily amount was 280 cc., while during the dosing period the average was 360 cc. Still another (XV) passed a daily average of 300 cc. before dosing, but this was increased to 460 cc. when thallium was given. The tear glands are likewise stimulated; several dogs wept continuously and thallium was detected in the secretion. The secretion of bile was apparently excited; in all cases where post-mortem examinations were made the bile bladder was found gorged with bile, and in the toads the livers were discolored. All the dogs vomited more or less of mucus colored with bile which has also been found in the contents of the stomach after death. The whites of the eyes in several dogs were colored yellow. Whether these conditions are due to a true cholagogic action is yet open to question. There were no evidences, however, of any increased activity in the secretions of saliva, and no symptoms of salivation were noticed. Neither was constipation induced at any stage of the poisoning, and in the dog diarrhea always occurred. The poison evidently exerts some aphrodisiacal action, since in three of the dogs the organ involved was constantly erected. Small sores and pus sacs were found on three dogs in the pelvic region. The purplish
blue line observed on the gums may be due to a deposition of thallous sulphide, since the similar blue line found in lead poisoning has been ascribed to a deposit of the sulphide of the metal.

The last symptom to appear is the difficulty in respiration. This trouble is only slightly felt at first but gradually increases, so that a short time before death the subject fights desperately for each breath. During this period the heart beats slowly but strongly. Finally, however, a climax is reached in this spasmodic gasping for breath, the subjects become quiet and all muscular effort ceases, inspirations occur at longer and longer intervals, becoming so slight as to be scarcely noticed, and finally cease altogether. In nearly all cases death has occurred very quietly and coma has preceded the end by several hours. The direct cause of death was plainly due to asphyxia induced by an inhibition of respiratory impulses. There was no indication of heart failure, and in the toads the heart was in every case found beating many minutes after breathing had ceased and when the animals were partly dissected. The labored respiration was especially striking in the case of the fishes, several subjects making the most violent motions with the head at each effort to breathe.

The albuminuria which begins a day or two after such small doses as 30 mg. in a dog has been a consistent symptom. At first the amount of albumin is very slight, but it increases in quantity until excessive amounts are excreted daily.

In the whole list of experiments it is a remarkable fact that none of the subjects gave any expression of suffering. There was no whining nor moaning heard from any of the animals. In view of the extensive and oftentimes extreme congestion of the alimentary tract this fact points to greatly diminished sensibility. In fact, all classes of subjects became dull and stupid and for some time before death were in a more or less comatose condition. In none of the injected subjects was there any local swelling or soreness at the point of injection nor any hardening of the tissues due to precipitated proteins. Neither was there any discoloration of skin or hair noticed in any subject and the skin of one of the writers was unaffected by small amounts of various salts rubbed in. Excessive loss of hair was observed in all dogs which were kept under observation for a prolonged period after the administration of thallium salts, thus bearing out a symptom already noted on human patients.
The great similarity of the symptoms in thallium poisoning to those induced by lead is evident. With both poisons the lower limbs are affected with lack of coordination and paralysis. There is the same loss of appetite, the abdominal region is constricted and there is notable congestion in the intestines. In both cases much hair is shed, and a colored line (blue with lead, purplish blue with thallium) is found on the gums. Emaciation and conjunctivitis are common to both forms of intoxication, while general nervous disorders (lead palsy) are induced by both metals.

With lead, however, constipation is the rule and sometimes this is the only symptom developed by medicinal doses. Diarrhea occurs but is rare, as is also vomiting, which usually occurs only when large doses which act as an emetic have been taken. Also in plumbic poisoning the urine is scanty and frequently suppressed. With thallium diarrhea is always present and vomiting is the rule. This last is induced and persists many days after the last dose of the poison has been given, and hence there can be no emetic-like action in these vomitings. The urine also for some days is largely increased in quantity, and contains much albumin and large sediments in which casts are not uncommon. This is usually followed by an irregular secretion and even suppression of the urine in the last stages of the disorder. Such conditions suggest a probable breaking down of the secretory mechanism of the kidneys. And in this connection it is of interest to note that the symptoms which are observed in the later stages are almost identical with those which accompany uremic intoxication. Herter has described a large number of cases of which most were characterized by apathy, gradually passing into tremors, conjunctivitis, depression of temperature, severe vomiting and diarrhea, with extensive inflammation of the stomach and intestines. Dyspnea finally appears, coma intervenes, and death results generally from respiratory failure.

These symptoms are precisely those which ultimately arise in thallium poisoning. It is significant that they do not present themselves for some time (two to five days) after the metal has been administered, and that the respiratory disturbances appear

1 Contributions to Medicine by Pupils of Dr. Welch, p. 69.
only in the last days of the poisoning, while the more immediate effects, such as loss of coördinated movement in the hind limbs, apparently due to the more direct action of the thallium itself, appear very soon after the substance is administered. Yet the examination of sections of the kidney of one of the dogs (XV) showed in that case lesions hardly severe enough to produce a uremic condition. Thus the idea that an artificial nephritis may be induced by thallium or that uremic intoxication was the direct cause of death in the animals experimented on, is open to question. The writers hope soon to be able to report the structural changes in the kidneys of a number of cases of thallium poisoning with a view to arriving at a positive conclusion on this point.

A later paper will present the chemical data secured in the course of this work, bearing especially upon the influence of thallium upon nitrogenous metabolism, its distribution in the organism, and its excretion.

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THE TOXICITY OF THALLIUM SALTS:
First Paper
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