An experimental study of lithium / by Clarence A. Good.

An Experimental Study of Lithium.

BY

CLARENCE A. GOOD, M.D.,

ASSISTANT IN PHARMACOLOGY, UNIVERSITY OF MICHIGAN.

FROM

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES,

FEBRUARY, 1903.

Extracted from The American Journal of the Medical Sciences, February, 1903.

AN EXPERIMENTAL STUDY OF LITHIUM.*

By Clarence A. Good, M.D.,
Assistant in Pharmacology, University of Michigan.

Lithia was discovered by Arfwedson, in 1817, in the mineral petalite. Since that time lithium has been shown to be widely distributed in nature, but occurring only in small quantities. It occurs in various minerals, in mineral waters, in sea water, in the ash of plants, and in some vegetables used as foods. It has also been found in the ashes of blood and milk. It always occurs in combination as an oxide, chloride, silicate, or fluoride, with potassium and aluminum. Lithium belongs to the group of alkalies and has an atomic weight of only 7 +.

Lithium seems to have been first introduced into medicine by Sir Alfred Garrod[1] about the year 1863, for the cure of gout and rheumatic gout. The reason for its introduction was that lithium was found to be an excellent solvent for uric acid and the urates in experiments, and it was supposed that by giving the substance the deposits in and around the joints could be disposed of and further deposits prevented. Lipowitz,[2] in 1841, was one of the first to show the marked affinity of lithium salts for uric acid, showing that it formed an acid salt soluble in sixty parts of water at 122° F. In 1843 Dr. Alex. Ure[3] found that a urinary calculus composed of alternate layers of uric acid and oxalate of lime when placed in a solution of 4 grains of lithium carbonate in one ounce of water and maintained at blood heat for five consecutive hours lost 5 grains in weight. Thinking that if one could thus lessen the size of urinary calculi in a few hours it would be an easy matter to entirely remove them from the bladder, he advised the injection of solutions of lithium into the bladder for the cure of stone. In practice this was found to be unsuccessful, and it is interesting to note that the trial *case* in which Dr. Ure used the injections afterward came to operation and died.[4] Dr. Ure then showed that one must be very careful in the injection of lithium solutions into the bladder, for if any sodium phosphate be present the insoluble lithium phosphate is formed.

* Read before the Ann Arbor Medical Club, May 14, 1902.

To show the effects that lithium carbonate had on the sodium urate in gouty deposits, Garrod made the following experiments:

A metacarpal bone having the phalangeal extremity completely infiltrated with gouty deposits was placed in water to which a few grains of lithium carbonate were added, and in the course of two or three days no deposit could be seen, and the cartilage seemed to have been restored to its normal state. Similar experiments made with sodium and potassium carbonates did not show any marked solution of the urates. It was reasoning from such experiments as these that lithium was introduced into medicine as a cure for gout. Of course, the fallacy of the treatment lies in the fact that lithium is a solvent for uric acid and urates only when in concentrated solution as well as in considering the diminished excretion of uric acid and urates as the chief pathological condition in gout.

To show that lithium in dilute solution was not a solvent for uric acid, Krumhoff[5] made the following experiments. To show the solubility of uric acid in distilled water at body temperature, he weighed out 0.5 g. of the pure acid and placed it in a flask containing 200 c.c. of distilled water. Four other flasks were similarly prepared. These were now placed on a water-bath so fixed that the flasks were completely covered in, and only a space was allowed for the thermometer to descend. The water-bath was at 39.5° C., and the flasks at 37.5° to 38.5° C. The heating was kept up for six hours. The flasks were then taken out, allowed to cool, the undissolved uric acid filtered off and thoroughly washed, dried, and weighed, when it was found that the 200 c.c. of water at body temperature had dissolved 0.0217 grain of uric acid. These experiments were confirmatory to similar ones done by Jahns,[6] who found 200 c.c. to dissolve 0.0214 grain in eight hours.

To show the solvent action of lithium chloride the following experiment was done: To 200 c.c. of water containing 0.5 grain of lithium chloride 0.5 grain of uric acid was added and placed on the water-bath under conditions similar to those in the last experiment, and heated for six hours. The undissolved uric acid was then filtered off, washed, dried, and weighed. Four other similar experiments were made, and the average of these showed that only 0.0118 grain of uric acid had been dissolved as against 0.0217 grain dissolved by distilled water under similar conditions. That lithium salts are solvents for urates and uric acid only when in concentrated solutions is not generally taken into consideration, and the majority of those who now administer lithium salts do so with the idea that they are uric acid solvents. The statements made as to the amounts of urates and uric acid eliminated after the use of the lithium salts vary greatly. Levy,[7] giving lithium bromide in gouty subjects, found the urates and uric acid diminished. Haig[8] and Oliver[9] found the uric acid diminished. Considering, how-

ever, that no constant diet was used, and also the faulty methods of estimation, these results can be considered of much value.

Dr. Garrod also claimed to have seen marked benefit derived from the external use of solutions of lithium salts applied to joints, even to the disappearance of small tophi. Hüfner,[10] to show that lithium salts were not absorbed through the skin, made a 1 per cent. solution of lithium chloride. This was warmed to 30° C., and one of his pupils placed both feet in this for thirty or thirty-five minutes, and, although Hüfner was able, by the use of the spectroscope, to detect the presence of lithium in solution in the proportion of nine-millionths part of a milligramme lithium carbonate per c.c., he could not demonstrate lithium in the urine in this and similar experiments, even after the urine for twenty-four hours was taken and evaporated.

Hüfner could not find lithium in the urine after taking 25 milligrammes, even when the urine for twenty-four hours was concentrated to 30 c.c., but after taking 35 milligrammes, lithium could be plainly demonstrated in the urine two hours afterward.

The lithium salts are rapidly absorbed from the stomach. Dr. Bence Jones[11] gave an animal 3 grains of lithium chloride on an empty stomach and detected lithium in the aqueous humor of the eye and in the cartilage of the hip-joint fifteen minutes afterward. He gave 7 grains to a parturient woman eight hours before delivery, and found lithium in the umbilical cord. He also records giving 20 grains to a patient three and a half hours before an operation for cataract, and at operation traces of lithium could be detected in the lens. Four days later it could be detected in the secretions, and was not wholly eliminated till the seventh day. I have detected lithium in the saliva within eight minutes and in the urine and feces within ten minutes after injecting 1 grain subcutaneously in a cat.

The effect of lithium salts on animals was studied as early as 1868 by Rabuteau.[12] As a result of his experiments he concluded that lithium was a harmless metal, being less poisonous than potassium. He noted, however, that 20 grains of lithium sulphate given to a dog caused vomiting and evacuation of the bowels. He only observed the dog for a few hours and does not state the final results. In 1873 James Blake[13] experimented with lithium, and concluded that lithium, sodium, rubidium, tellurium, and cæsium are equal in their action, and that the amount of lithium sulphate necessary to kill rabbits was 1 grain per kilo.

In 1875 Hesse[14] experimented with lithium on frogs, rabbits, and doves. He found that lithium chloride injected into a vein caused diastolic stopping of the heart, while the nerves and muscles were yet excitable. He also found that in warm-blooded animals lithium salts decreased the excitability of the nerve centres, decreased the temper-

ature, and sometimes caused diuresis. Cash and Brunton,[15] experimenting with the metals on frogs, found that lithium, rubidium, and cæsium have a tendency to affect either the upper part of the spinal cord or the higher motor centres connected with the forelimbs, the reflexes disappearing sooner from the arms than from the legs, and that stiffness was noticed in the arms. They also found the motor nerves paralyzed to a greater or less extent by lithium and potassium.

In 1884 Krumhoff[5] made a careful experimental investigation of the effects of lithium on animals, and reviewed the literature thoroughly. He found that when a lithium salt was injected into the blood it depressed the heart's action and caused a fall of blood pressure, and if the dose was large enough stopped the heart in diastole. The dose of lithium salts necessary to stop the heart he found to be much larger than the dose of potassium salts necessary to produce the same effect. He also found that vomiting and diarrhœa were caused by its subcutaneous use, and the prolonged ingestion of small doses killed the animal sooner or later by causing a fatal gastro-enteritis.

The lesions found at autopsy were hemorrhages into the stomach and bowels, reddening and swelling of the mucous membranes, and sometimes small hemorrhages into the heart muscle. The prolonged use of small doses of potassium salts caused no such effects.

To carefully study the effects of lithium salts on animals and determine where it was excreted, I made thirty odd experiments on cats and dogs, administering the drug subcutaneously and by the mouth. The salt used in my experiments was the chloride, because of its easy solubility and because the carbonate, which is usually used therapeutically, is in part, at least, changed to the chloride in the stomach. A pure salt was used and was examined quantitatively for lithium, as well as titrated for chlorides, so that the dosage might be accurate.

The method of quantitative estimation which I used was as follows: The urine, saliva, or feces to be examined was evaporated to dryness and burned. This was then extracted, with a large amount of water, rendered acid by hydrochloric acid, filtered, and the filtrate evaporated to about 50 c.c. To this milk of lime was added and thoroughly rubbed up until alkaline in reaction. This was then filtered and thoroughly washed with water until the washings failed to show lithium by the spectroscope. To this solution ammonium carbonate in solution was added as long as a precipitate formed, filtered, and the filtrate washed with water till the spectroscope failed to show any lithium in the washings. This filtrate was now acidulated with hydrochloric acid and evaporated in a platinum dish to dryness, and heated to drive off the ammonia. The residue was dissolved in water acidulated with hydrochloric acid and evaporated to dryness. This residue consisted of potassium, sodium, and lithium chlorides, and as the chloride of lithium

is soluble in alcohol, while the chlorides of sodium and potassium are nearly insoluble, the dry salt was extracted with equal parts of absolute alcohol and ether. Comparatively small amounts were used, and the undissolved portion, after being washed with equal parts of alcohol and ether, was dissolved in water and examined by the spectroscope. If this showed the presence of lithium the process was repeated. In this way I was able to separate most of the sodium and potassium chlorides from the lithium chlorides. The alcohol-ether solution was now evaporated to dryness, dissolved in a little water, and a 10 per cent. solution of sodium phosphate added, 1.1 c.c. for each 0.1 g. of lithium excreted. This was now evaporated to dryness, whereby the soluble lithium chloride was changed to the insoluble lithium phosphate. To this a small amount of water was added, heated slightly, and an equal amount of strong ammonia solution added, and let stand for twelve hours in the cold. As the lithium phosphate is practically insoluble in the strong ammonia solution, while the phosphates of sodium and potassium are freely soluble, the undissolved portion was lithium phosphate. This was now filtered through a Goosh filter, washed with a solution of strong ammonia, and this first wash-water again run through for lithium. The Goosh filter was now placed in an oven, thoroughly dried, and the weight of lithium carbonate determined, which was calculated back to the chloride.

By this method the lithium phosphate always shows a strong sodium flame, and the results are probably high. Yet, by becoming accustomed to the method, fairly accurate results can be obtained.

Only a few experiments will be quoted in detail.

Experiment 31, March 21, 1902. Healthy cat, weighing 1650 g., was given 1 g. lithium chloride, well diluted, hypodermically, at 10.40 A.M. At 10.45, movement of bowels, hard-formed. At 10.48, vomited; consisted of mucus and undigested food. An examination of this by the spectroscope showed the presence of lithium. At 11.05, marked salivation. At 11.10, vomited. At 11.30, movement of bowels. At 2.30 P.M. the cat had passed two or three diarrhœal stools. She sat humped up in the cage, and would not stir. By 5 P.M. she had had two more movements of the bowels and had vomited once.

22d. At 9 A.M., cat very weak, unsteady on feet. Drinks, but will not eat. Several diarrhœal stools during the night. He passed some urine, but not a great deal. At 5 P.M., cat in about the same condition, although weaker.

23d. Cat much weaker. Unable to walk without tottering. Hind-parts seem most useless. Will not eat or drink. No stool or vomiting. About normal amount of urine.

24th. Cat died during the night.

Autopsy Findings. March 24th, 11 A.M. Weight, 1405 g. All the organs were normal in appearance, except the stomach and intestines. The mucous membrane of stomach was reddened, and in two places showed hemorrhagic spots the size of a small pea. Mucous membrane

of the small bowel not much inflamed, but covered with a thick, tenacious bile-stained mucus. The mucous membrane of the large bowel distinctly reddened and thickened, and contained two small ecchymoses. All the vomited matter, the stools, and the contents of the stomach and bowels were added together, and from them 0.086 g. lithium chloride was obtained. A microscopic examination was made of parts of the heart muscle, liver, kidneys, stomach, and intestines. The heart, liver, and kidneys showed no appreciable changes. Sections of the stomach and bowel showed a marked congestion. The mucous membrane was covered with a thick coating of mucus, and in places contained small hemorrhages.

Experiment 5, November 11, 1901. A healthy cat, weighing 3700 g., was given 2 g. lithium chloride, well diluted, hypodermically, at 1.35 P.M. At 1.40, watery stool. At 2.00, passed urine. At 2.10, vomited. At 2.20, washed out stomach. At 2.40, thin, watery stool. At 3.10, washed out stomach. At 4.00, washed out stomach. At 5.00 cat was killed with chloroform.

Autopsy. Stomach contained mucus and water, which were added to vomitus and stomach washings. No marked change in the stomach walls. Bowels empty, and showed no marked change. Liver, kidneys, lungs, and heart apparently normal. The vomitus and stomach washings were kept separate from the bowel contents and stools, and the lithium in each estimated. The former contained 0.125 g. lithium chloride and the latter 0.034 g.

Experiment 10, November 25, 1901. A healthy cat, weighing 1320 g., was given 0.5 g. of lithium chloride, well diluted, hypodermically, at 1.20 P.M. At 1.30, vomited several times; 1.40, profuse watery stool. Up to 4.00 had vomited several times and had several watery stools.

26th. 1.00 P.M. Cat seems quite normal. Has not vomited nor had movement of the bowels during the night. Has passed considerable urine. When taken out of the cage seems stiff and perhaps somewhat unsteady on her feet. She drinks, but will not eat.

27th. 1.00 P.M. Cat more feeble than yesterday. When taken from the cage she is so stiff and weak that she can hardly walk. Hindparts seem most useless. No vomiting. No stools. Will not eat or drink.

28th. 1.00 P.M. Cat the same, but weaker.

29th. 1.00 P.M. Cat extremely weak. Unable to walk. Seems to be unable to raise her hindparts. No stools or vomiting.

30th. Cat died during the night.

Autopsy. Cat weighed 1080 g. The lungs, heart, liver, and kidneys were normal. Mucous membrane of the stomach reddened and covered with a thick, bile-stained mucus. Two small ecchymoses into the mucous membrane near the pylorus.

Small bowel somewhat congested and covered with a thick, tenacious mucus. Otherwise normal. Large bowel deeply congested. Several areas of hemorrhage into the mucous membrane, which is greatly thickened. The vomitus was worked separately from the stools, and from the former 0.021 g. lithium chloride, and from the latter 0.026 g. lithium chloride was obtained.

Microscopic examinations of the various organs showed no evident changes in the lungs, heart, liver, and kidneys, while the changes in the stomach and bowel corresponded to those given under Experiment No. 31.

Experiment 9, November 22d. A healthy cat, weighing 2650 g., was given 1 g. lithium chloride, well diluted, hypodermically. This experiment is of interest chiefly in that the cat did not vomit, but was salivated profusely. This salivation was undoubtedly due to nausea, and was observed in many experiments before vomiting came on. All the saliva was carefully collected in a clean dish, and, as it showed lithium by the spectroscope, the amount was estimated quantitatively, and 0.021 g. lithium chloride was obtained from it. The cat died in three days with all the signs of gastro-enteritis, and from the stools, stomach, and bowel contents 0.110 g. of lithium chloride was obtained.

These experiments have been given in detail, because they show the essential symptoms and cause of death from lithium salt in whatever form or manner it be administered. From these experiments it will be seen that shortly after the administration of the lithium salt the animal is taken with nausea, vomiting, and diarrhœa, and dies sooner or later with all the characteristic signs and symptoms of gastro-enteritis, the progressive emaciation and weakness being wholly the result of the gastro-enteritis. The stiffness and inability to use the hindparts is also due to the weakness caused by the gastro-enteritis, and is seen in poisoning from the heavy metals, colchicum, and other drugs that cause a fatal gastro-enteritis. There is practically a total absence of nervous symptoms, although in a few cases slight tremors were noticed. This is of importance, as tremors have been noted in a few cases of poisoning in man.

From these experiments it will be seen that lithium is partially excreted in the saliva and into the stomach and bowels, though the quantity that can be reclaimed from these secretions is usually not great.

To show the effects of the prolonged administration of small doses hypodermically, the following two experiments may be given:

Experiment 12, December 3d. A healthy cat, weighing 3170 g., received each day for eighteen days 0.0567 g. lithium chloride, well diluted, hypodermically. She had diarrhœa on the second day, which was severe by the fourth day, when the stools were blood-streaked. The urine and stools were kept separate. The diarrhœa was severe, and she occasionally vomited. On the tenth day she had lost 500 g., or about one-sixth of her original weight. Her coat had lost its gloss, and her health and strength distinctly lessened. By the eighteenth day she was very weak, weighed 2650 g., had a severe diarrhœa, and, as it was quite evident that she would soon die, she was killed with chloroform, as I wished to examine the tissues in a perfectly fresh condition.

Autopsy Findings. The lungs, kidneys, liver, spleen, and heart were apparently normal.

The stomach did not show any marked changes. The upper part of the small intestines was quite normal, but the lower one-fifth, together with the large bowel, was deeply congested. The mucous membrane was thickened and showed numerous small and large hemorrhagic areas. There were two small superficial ulcers in the large bowel, which was more severely affected than the small bowel, and, I may add,

that this is unfortunately the case when small doses are administered, whether given subcutaneously or by the mouth. The stools and urine for the first ten days were examined for lithium. During this time she had been given 0.567 g. lithium chloride. From the bowels 0.039 g., and from the urine 0.228 g. of lithium were obtained.

Experiment 14. In order to accurately collect the urine a healthy female dog, weighing 8.2 kilos., was operated upon, the perineum being cut so that she could be easily catheterized. After the wound had thoroughly healed, and beginning February 7th, she was given 0.62475 g. of lithium chloride, hypodermically, daily. She was not allowed to pass any urine, being catheterized frequently enough to prevent this. The urine and stools were kept separate. At the end of ten days her weight was 8.1 kilos., and she was lively, ate and drank well, and apparently had not suffered from the injections. From the ten days' urine 0.383 g. lithium chloride was obtained, and from the feces 0.074 g. of lithium chloride. She had received in this time 0.62475 g. of lithium chloride.

The same dose was continued eight days longer, and at this time she began to show symptoms, such as loss of appetite and a slight diarrhœa. On the eighteenth day she weighed 7.9 kilos. Her coat was roughened, and she was evidently in poorer condition than at the beginning of the experiment.

The injections were then stopped until February 4th, when they were again taken up, increasing the dose to 0.2479 g. From the second day on she vomited occasionally, usually consisting mostly of mucus. There was a slight diarrhœa. Her appetite was very poor. The injections were continued for six days. At the end of this time her weight was 7.1 kilos. From the six days' urine 0.589 g. and from the feces 0.014 g. lithium chloride was obtained. During the six days she had been given in all 1.5 g.

The injections were now increased to 0.62475 g. daily. This was continued for five days. During this time she vomited several times a day and had a severe diarrhœa, the stools being often streaked with blood. She ate scarcely anything, and at the end of the experiment weighed 7 kilos. She was very weak and emaciated. Coat rough and lustreless.

From the five days' urine 1.49 g. and from the feces 0.128 g. of lithium chloride was obtained. During the five days she had received 3.1 g. The injections were now stopped, but the vomiting and diarrhœa continued unabated. The appetite was completely lost, and she became weaker daily. On February 24th she was so weak that she was hardly able to stand, and as it was evident that she would soon die, she was killed with chloroform. At this time she weighed 6.8 kilos. At the beginning of the experiment she had weighed 8.2 kilos., a loss of 1.4 kilos in weight.

Autopsy. Heart showed a few small hemorrhages under the endocardium, otherwise normal. Lungs, liver, and kidneys normal. The walls of the stomach were greatly thickened and reddened, and contained several small hemorrhages. The mucous membrane of the whole bowel was thickened and reddened, though this change was most marked in the large bowel. The lower part of the large bowel contained a few small ulcers and numerous ecchymoses.

Microscopic examination of the heart showed only a few small hem-

orrhages under the endocardium. Lungs, liver, and kidney showed no marked changes. The examination of the stomach and bowel showed congestion and thickening of the mucous membrane, with a superficial layer of mucus and detritus, and one or two small superficial ulcers.

One hundred grammes of the muscle from the ham were burned and the ashes dissolved in 30 c.c. of distilled water. This gave a distinct spectroscope of lithium, even when diluted to 90 c.c. One hundred grammes of normal dog's muscle when burned and the ashes dissolved in 30 c.c. gave no lithium spectroscope, even when concentrated to 5 c.c.

The ashes from 100 g. of blood taken from this dog showed lithium, even when diluted to 130 c.c. That from normal dog's blood gave only a faint spectroscope when dissolved in 5 c.c. water. It is evident from this that lithium is slowly excreted and is stored up in the body. The liver did not show as much lithium as an equal weight of muscle.

When lithium salts are given by the mouth they produce essentially the same symptoms and changes as when given hypodermically, though, of course, larger doses are required. Cats, after receiving 0.5 to 2 g. by the stomach, vomit two or three times, but otherwise are very little affected, though frequently some diarrhœa is noticed. On the contrary, when small doses are administered daily by the mouth, cats and dogs show first diarrhœa, with some blood in the stools, vomiting, loss of appetite, and weight, and finally die from the gastro-enteritis, as the following experiment well shows:

A healthy cat, weighing 2000 g., received daily for the first six days 0.062475 g. by the stomach. No symptoms at this time, though she had lost 100 g. in weight. The dose was now increased to 0.125 g. daily, which was continued for five days; during this time she developed a moderately severe diarrhœa, and at the end of six days weighed 1800 g. The dose was now increased to 0.188 g. daily, and was continued for fifteen days. During the most of this time she had a severe diarrhœa, the stools often containing blood, and during the latter part of the period she was nauseated, and vomiting constantly, and finally died of gastro-enteritis and exhaustion, weighing 1500 g. At autopsy there was found a marked inflammation of the whole gastro-intestinal tract. This was most severe in the large bowel, which contained many large and small ulcers and ecchymoses. There was also some enlargement of the abdominal lymph glands and two or three small abscesses in the liver, undoubtedly secondary infections from the bowel.

In some experiments the animals that were given lithium in small doses lost over one-third of their weight, and finally died of exhaustion and gastro-enteritis. Sixty milligrammes of lithium chloride per kilo. daily always killed dogs and cats sooner or later from gastro-enteritis. Though frequently, especially in dogs, this was much delayed by the animals vomiting the lithium solution soon after taking it.

The cause of this gastro-enteritis is undoubtedly connected with the excretion of the metal through the bowel wall. This action on the bowel is not peculiar to lithium, but is caused by many other substances, among which may be mentioned mercury, arsenic, colchicum, emetine, and aloin. These substances are excreted by the bowel, and also in the urine, and induce irritation or inflammation at the point excreted. This may be because they collect in larger quantities in the excretory organs, or because they are here freed from some harmless combination in which they have circulated in the tissues. At times the bowels are most affected, and *at other* times the kidneys suffer most. Lithium salts are slowly excreted by the kidneys and do not seem to cause any appreciable amount of renal irritation. On the contrary, the excretion through the bowel causes marked irritation and inflammation. The percentage of lithium salts obtained from the feces in my experiments was always greater in those cases accompanied by marked vomiting and diarrhœa.

There are very few cases mentioned in the literature of poisoning from the use of lithium, and it is not generally considered as inducing any deleterious symptoms. Wood, in his text-book of *Therapeutics*, says he has seen a twenty-grain dose of lithium carbonate produce a severe general prostration in a feeble adult female; and Hare, in his *Practical Therapeutics*, says: "It is worthy of note that in some cases citrated lithium will disorder the stomach and produce vomiting." In a note to the French edition of Garrod on *Gout*, the statement is made that small doses are readily borne, but doses of thirty to fifty grains of the carbonate give rise, after a few days, to cardialgia and dyspepsia. Rabuteau states that 15 to 30 g. per diem often causes dyspepsia, and even vomiting Climent[17] records similar results in his own person, and Althaus[18] states that lithiated waters, if taken in large amounts, give rise to sickness and diarrhœa. Kolipinski[19] reports two cases of marked tremor following the use of lithia tablets. This was also accompanied by marked general prostration and weakness. The condition disappeared in three or four days. Considering the marked effect of lithium salts on animals, it is surprising that symptoms on the part of the gastro-intestinal tract have not been noticed more frequently. It is not improbable that such symptoms have frequently been noticed, but have not been reported, or have been considered as due to other causes. It might be stated here, however, that lithium is frequently given as the natural lithia waters, which, as shown by the analyses of Harrington,[20] Waller,[21] and others contain only very small amounts of lithium, many containing none at all.

Lithium salts are frequently credited with the possession of diuretic action. To determine whether they possessed any marked diuretic action I made several experiments on rabbits, as follows: Large

rabbits were anæsthetized with urethane and paraldehyde. A canula was introduced into the jugular vein and one into the bladder, so as to be able to inject the fluids into the blood and to collect the urine.

After determining the normal flow of urine, warmed solutions of equal strength of lithium chloride and sodium chloride were injected into the vein and the urine collected and measured. In order to have the solutions contain equal numbers of molecules, they were so prepared that their freezing points were the same. Solutions containing about 3 g. and 6 g. of lithium chloride and sodium chloride, respectively, in 100 c.c. of distilled water were used, and from 30 to 50 c.c. were injected at the rate of 15 c.c. in five minutes. The results of these experiments did not show that solutions of lithium chloride caused any greater diuresis than solutions of sodium chloride.

The salt of lithium used in medicine is the carbonate. It is much less soluble than the chloride, and experiments on animals show that it produced the same effects as the chloride. The bromide of lithium has been used in the treatment of gout, epilepsy, and other nervous diseases. Dr. Weir Mitchell,[21] after using lithium bromide in several cases, concluded that it was as efficient as sodium or potassium bromide, and that its influence over insomnia was greater.

Fontan[22] found lithium bromide to possess the same sedative action as potassium bromide, but he thought it less liable to cause untoward symptoms. Dr. Mitchell, however, saw skin rashes following the use of lithium bromide. Lévy[24] found lithium bromide to possess marked sedative action, and to be less depressing to the heart than potassium bromide. He did not, however, find it to be of any special value in gout.

Since the atomic weight of lithium is so small, there is, of course, more of the bromide ion in lithium than in an equal weight of potassium bromide, and the action of the bromide ion completely overshadows the action of the lithium ion. Lithium bromide does not possess any advantages over the commonly used potassium bromide.

Conclusions. 1. Lithium is excreted in the saliva, into the stomach and bowel, and in the urine. The greater amount is excreted in the urine, though more appears in the stomach and bowel when nausea, vomiting, and diarrhœa have been profuse. It can usually be demonstrated in the secretions within ten minutes after a hypodermic injection, though its excretion proceeds slowly, for I have found it in the secretions twenty-three days after the injections were stopped.

2. Lithium salts given to animals, hypodermically or by the stomach, cause, sooner or later, fatal gastro-enteritis. This gastro-enteritis is, undoubtedly, connected with the excretion of the metal through the bowel wall.

3. Lithium salts do not possess any diuretic action that cannot be

accounted for by their salt action. They render the urine alkaline, and thus act like the other alkalies.

4. Lithium carbonate, in fifteen to twenty-grain doses, and lithia tablets have been known to cause gastro-intestinal symptoms in man.

5. Dilute solutions of lithium salts are not solvents for uric acid or urates.

Bibliography.

1. Gout and Rheumatic Gout by Garrod. Second edition, pp. 419–428.
2. Ann. d. Chem. u. Physiol., Bd. xxxviii. S. 348.
3. Pharmaceutical Journal, August, 1843.
4. Lancet, 1860, vol. ii.
5. Wirkung des Lithium, Inaugural Dissertation, Göttingen, 1834.
6. Arch. d. Pharmac., 1883, Bd. xxi. H. 7.
7. Gazette Médicale de Paris, Nov. 27, 1875.
8. Uric Acid in Causation of Disease, p. 54.
9. Lead Poisoning, p. 107.
10. Ztschr. f. Physol. Chem., vol. iv. pp. 378–381.
11. Lectures, p. 16. Quoted in Phillips' Materia Medica, vol. ii. p. 228.
12. Études experimentales sur les effects physiologiques des fluorures et des composis metalliques en général. Paris, Germer Baillière, 1867.
13. California Academy of Sciences.
14. Inaugural Dissertation, "Lithion," Göttingen, 1876.
15. Phil. Trans. Roy. Soc., 1884, p. 222.
16. Quoted in Phillips' Materia Medica and Therapeutics, vol. ii. p. 228.
17. Paris Thèse, 1874. Traitement de la Gravelle.
18. Maryland Medical Journal, vol. xl., No. 1.
19. Boston Medical and Surgical Journal, 1896, vol. cxxxv. p. 644.
20. Journal of the American Chemical Society, 1890, vol. xii. p. 214
21. The American Journal of the Medical Sciences, vol. lx. p. 443.
22. Du Bromure de lithium, Nancy, 1825, No. 4.
23. Essai sur l'action physiologique et therapeutique du bromure de lithium. Paris, 1874, No. 4.

Lea's Periodicals.

The Medical News—Weekly.

A weekly medical newspaper is indispensable to those who would keep always posted to date on the incessant advances of practical medicine. The News answers every need. Its many departments cover all avenues of information and present a comprehensive knowledge of progress in every line. Weekly, illustrated, 2496 quarto pages of reading matter per year. Price, $4.00.

The American Journal—Monthly.

A monthly medical magazine, covering the entire science, and therefore helpful to every practitioner. Its Original Articles represent the experience of the most progressive medical men, its Reviews keep readers discriminatingly posted on the best literature, and the department of Progress is an authoritative and instructive summary of advances thoroughly digested from the leading medical periodicals of the world. Monthly, illustrated, 2304 pages of reading matter per year. Price, $5.00.

Progressive Medicine—Quarterly.

Progressive Medicine consists of original matter written by authorities in their respective departments, who give in an interesting narrative form a clear statement of the world's advances in every branch. Issued every three months it brings to the reader at frequent intervals fresh knowledge ready for application. Quarterly, illustrated, 1600 to 2000 pages per year. Price, $10.00, for the four volumes in cloth binding.

The Pocket Formulary for 1903.

The Medical News Formulary contains about 1700 prescriptions representing the latest and best therapeutics. Arranged alphabetically under headings of the various diseases for quick reference. Full annotations, directions and details. A most useful wallet-sized volume leather bound, with pocket and pencil. $1.50, *net*.

The Visiting List for 1903.

The Medical News Visiting List contains 32 pages of data needed by every practitioner and blanks for recording all details of practice, both clinical and financial. In four styles: Weekly, dated for 30 patients, Monthly, undated, for 120 patients per month, Perpetual, undated, for 30 patients weekly, and Sixty Patients, undated and without the preliminary data, for those requiring specially large record books. Price, $1.25. Thumb Index, 25 cents extra.

Special Combinations.

These unrivalled periodicals and practical aids and conveniences are offered in combination on reduced and easy terms. Sample reductions are given below and rates will be quoted on any other combinations on application. Orders in excess of $4.00 can be divided into convenient instalments, concerning which address the Publishers.

Per Annum.	Alone.		In Combination.		
American Journal of the Medical Sciences,	$5.00	$8.00	$16.00	$16.75	$17.00
Medical News,	4.00				
Progressive Medicine,	10.00				
Medical News Visiting List,	1.25				
Medical News Formulary,	1.50 net,				
	In all $21.75 for $17 00				

LEA BROTHERS & CO., Publishers,

111 FIFTH AVENUE, NEW YORK. 706, 708 & 710 SANSOM ST., PHILADELPHIA.