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THE PHARMACOLOGY OF THALLIUM AND ITS USE IN RODENT CONTROL
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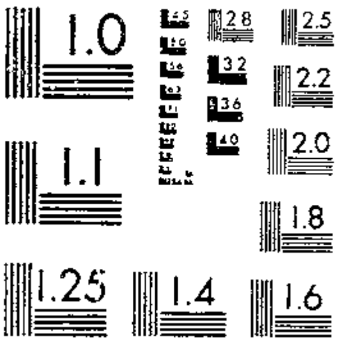

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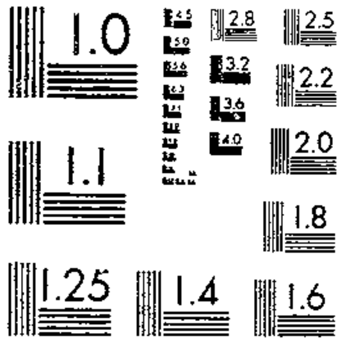

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TECHNICAL BULLETIN No. 238 — APRIL, 1931

UNITED STATES DEPARTMENT OF AGRICULTURE
WASHINGTON, D. C.

DEPOSITORY
SCIENCE & INDUSTRY DEPT.
APR 30 1931

# THE PHARMACOLOGY OF THALLIUM AND ITS USE IN RODENT CONTROL[1]

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## INTRODUCTION

The use of thallium as a rodent poison apparently originated about 1920, when a company in Germany introduced a proprietary rat poison that had thallium as its toxic principle. Very few reports upon its action were found in the literature previous to July, 1924, when samples of poisoned grain and rat paste were obtained from this company for study. Preliminary examination showed that these products were toxic to wild and to white rats and led to an investigation of the minimum lethal dose of thallium salts when fed to white rats and when intravenously injected into rabbits.

In August, 1925, the authors conferred with a representative of this company regarding the nature, mode of action, and use of its product in Germany and concerning plans for introducing it into the United States. The product was thoroughly discussed, and certain mimeographed circulars and information, as well as the company's method of chemical analysis, were submitted by the representative.

Thallium compounds were introduced into use for the control of rodents, particularly certain species of prairie dogs and ground squirrels that had refused to take strychnine baits. Arrangements

[1] The experiments here reported upon were instituted as a cooperative project between the then Bureau of Chemistry and the Bureau of Biological Survey prior to the appointment of the senior author as consulting pharmacologist with the Biological Survey, following his service in the pharmacology laboratory of the Bureau of Chemistry, now part of the Food and Drug Administration.

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were made with two American companies to supply the poison in commercial quantities. A number of reports by field agents of the Bureau of Biological Survey have already indicated the value and use of thallium products in field practice. The difficulties encountered by E. E. Horn, district investigator in the control-methods research project of the bureau, in obtaining acceptance by rodents of certain thallium baits led to the study of six commercial thallium products.

The methods employed in the feeding tests are essentially the same as those used in the previous pharmacological and toxicological studies of other rat poisons (arsenic, strychnine, barium carbonate, and squill) undertaken cooperatively by the Bureau of Biological Survey and the pharmacology laboratory of the Bureau of Chemistry (now the pharmacology unit of the Food and Drug Administration). The literature on thallium through 1896 was listed by Doan (*63*).[2] In the present bulletin, all available information in the literature has been consolidated, as well as the results of the feeding experiments with thallium compounds conducted by authors. So far as possible the original articles have been consulted.

## REVIEW OF THE LITERATURE ON THALLIUM

### OCCURRENCE AND PROPERTIES

Crookes (*53*) extracted thallium with selenium from the deposit of a sulphuric-acid factory at Tilkerode, in the Harz Mountains, Germany. When examined spectroscopically, a new spectrum was obtained in which a green line at 1442.6 on the Kirchhoff scale, corresponding to $\lambda = 5{,}350.7$ Å, was the outstanding characteristic. Since the green line recalled the fresh color of vegetation in spring, Crookes named the new element "thallium" from the Greek θαλλός (a young shoot). This discovery was announced in 1861. Lamy, two years later (*94*), observed the green spectral line from the sulphuric-acid deposit at Loos, France, where Belgian pyrites were roasted. He claimed that 0.000,002 milligram of thallium could be detected by its flame spectrum (*107*).

Uncombined thallium has not been found. It has been estimated that the hydrosphere and lithosphere of the earth contain less than one part of thallium per billion, and it is not shown in the solar spectrum (*107*). Lorandite ($TlAsS_2$), from Macedonia, contains 59.5 per cent of thallium associated with realgar. Urbanite, from Macedonia, contains 30 per cent of thallium. Hutchinsonite, a sulpharsenide of thallium, lead, silver, and copper, contains an appreciable quantity of thallium. The Swedish mineral crookesite, with a composition agreeing with $(Cu, Tl, Ag)_2Se$, contains 16 to 18.5 per cent of thallium. Fractions of 1 per cent have been reported in cupriferous pyrites from various sections of the world; and also in lepidolite, zinc blende, pitchblende, pyrolusite, manganite, carnallite, certain mineral waters, natural sulphur, and many minerals. It has been obtained from lead-chamber deposits in the manufacture of sulphuric acid by the roasting of pyrites or raw sulphur (*88*, *108*).

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[2] Italic numbers in parentheses refer to Bibliography, p. 21.

Lamy obtained thallium by neutralizing the slime in the lead chamber of a sulphuric-acid plant with lead oxide or calcium oxide and extracting with hot water. The solution was concentrated, and thallous chloride was precipitated by the addition of hydrochloric acid. After washing with dilute hydrochloric acid, the product was decomposed with sulphuric acid, and impurities were removed by hydrogen sulphide. The filtrate was concentrated and metallic thallium precipitated by zinc or by electrolysis. Thallium has also been obtained by extraction by sodium carbonate, precipitation of thallous sulphide in the presence of potassium cyanide, oxidation to sulphate, and precipitation with zinc. The precipitated metal is fused in a stream of hydrogen or in the presence of oxalic acid to prevent oxidation. A number of various modifications of these methods have been suggested (*66*, *84*, *87*, *107*).

Thallium is a soft, white metal with a grayish tinge, resembling tin in appearance. When exposed to the air, a dark-gray film of oxide rapidly forms, which is soluble in water. On paper the metal makes a mark resembling that produced by metallic lead. It has a specific gravity of 11.8, is somewhat softer than metallic lead, and is very malleable. Its chemical symbol is Tl, and its atomic weight 204. Thallium forms two series of salts—thallous compounds, in which the metal is monovalent, and thallic compounds, in which it is trivalent. By treating the metal, the oxide, or the hydroxide with the proper acid, a series of salts is obtained. These are usually white crystalline products, soluble in water.

Thallic salts are reduced to thallous salts on boiling, which process precipitates insoluble thallic hydroxide. Microscopically, 0.0016 milligram of thallium has been detected by precipitation of thallous chloride and 0.003 milligram by precipitation by yellow thallous iodide. Thallous sulphide ($Tl_2S$) is incompletely precipitated by hydrogen sulphide in the presence of mineral acids and completely precipitated in the presence of acetic acid. The sulphide is not soluble in ammonium sulphide (*107*, *108*, *122*). The existence of a number of sulphates has been claimed (*107*, *108*). Pale-yellow thallous chloroplatinate is precipitated on the addition of hydrochloroplatinic acid, and it is claimed that this reaction will detect 0.000,008 milligram of thallium.

Thallium has been employed in the manufacture of optical glass and in the electric-lamp industry. The acetate, the sulphate, and the nitrate have been used in medicine.

## DETERMINATION

Thallium may be qualitatively determined by the characteristic green line in the spectrum (*53*, *100*, *107*), as well as by chemical methods (*133*). The detection of 0.000,008 milligram of thallium by precipitation with chloroplatinic acid has been reported. Olmer and Tian (*114*) claim that the limit of detection with a spectroscope is 1: 500,000,000 (0.002 milligram per liter, or 2 parts per billion). In a Marsh apparatus, a stain is produced somewhat similar to an arsenic stain; however, the thallium stain produces a yellow color with iodine and is insoluble in ammonium sulphide.

The quantitative method of determination as furnished by the German company is as follows:

About 1 gram of paste or 2 grams of grain is weighed and intimately mixed with 15 to 20 grams of sodium carbonate (anhydrous) in a 70 c. c. porcelain crucible.

Heat for 1½ hours just under fusion temperature. Cool and transfer contents of crucible to a beaker or Erlemeyer flask containing 50 c. c. of water. Wash the crucible thoroughly with dilute hydrochloric acid and add the washings to the flask. When all the sodium carbonate has been decomposed with hydrochloric acid, a large excess is added (about 20 to 25 c. c.) and the liquid heated to boiling. Potassium chlorate is added slowly until probably 2 grams has been added and the liquid smells strongly of chlorine.

Evaporate till salt separates, add more water (150 c. c.), and evaporate again. Be sure that no free chlorine is in the liquid. Cool and add 10 to 15 c. c. of N/10 sodium thiosulphate and 1 gram of potassium iodide. Let stand 5 minutes and titrate the thiosulphate with N/10 iodine solution.

Calculation:

$$\frac{40{,}000{:}508 = \text{No. c.c. } Na_2S_2O_2.5\,H_2O{:}x}{\text{Weight of sample in grams}} \times 100 = \text{per cent } Tl_2SO_4$$

This method gives good results and requires no particular skill to operate.

## ACTION OF THALLIUM ON BACTERIA

Buschke and Jacobson (*23*) reported in 1922 that thallium has a strong oligodynamic action on *Bacillus coli*, typhoid and dysentery bacteria, streptococci, and staphylococci, but not on molds. When a piece of metallic thallium is placed in the center of an agar plate containing viable organisms, a clear zone of dead bacteria is produced over an area 7 to 14 millimeters in diameter. This action disappears when air is removed, but returns upon reexposure, a result suggesting that air oxidizes Tl to $Tl_2O$, which dissolves to form TlOH (*21*). Concentrations of thallium acetate or carbonate as strong as 1:1,000 (1,000 milligrams per liter) are required to inhibit the growth of *Bacillus coli*.

The cost and the scarcity of metallic thallium prevent commercial application of this property.

## ACTION OF THALLIUM SALTS ON ANIMALS

### GENERAL ACTION

Lamy (*94*), who was working upon thallium in France at the time Crookes discovered it in England, offered milk containing 5 grams of thallium sulphate to two young puppies; they drank only a small quantity, then refused to drink the remainder. In spite of every effort to save them, both died in four days. Six ducks, two hens, and a dog consumed a portion of the milk solution. During the day the dog became restless, salivated, and refused food; during the night, constipation and respiratory distress developed. The hind limbs of the dog and the legs of the ducks and hens became paralyzed. All animals died or were moribund 64 hours after taking the milk thus treated. Ten milligrams of thallium sulphate killed another dog in 40 hours, with manifestation of the same symptoms.

Grandeau (*80*) found in 1863 that 1 gram of thallium sulphate killed a dog in five days with all the symptoms of lead poisoning, whereas in another dog 1.5 grams of lead acetate caused emesis, but with eventual recovery. This led Paulet (*117*) to the conclusion that thallium was more toxic than lead.

In Blake's (*9*) experiments in 1890, 90 milligrams of thallium sulphate, intravenously injected into the jugular vein of a rabbit, stopped the pulmonary circulation for a few seconds, and a second dose killed; injected into the carotid artery, doses up to 350 milligrams were apparently inactive, but 750 milligrams killed by stoppage of pulmonary circulation. Small doses of thallium salts were tolerated for some time, but the effects were cumulative. Impairment of appetite, emesis, and diarrhea, followed by obstinate constipation, hemorrhages, tremors, lack of muscular coordination, conjunctivitis, general debility, and depression of respiration and circulation, were produced in animals. Post-mortem examination showed effusions of blood into the lungs, congestion of the gastro-intestinal tract, pericardial effusions and ecchymoses of the surface of the heart. Thallium was eliminated in all secretions.

Jones (*89*) demonstrated the presence of thallium in the urine of rabbits two hours after oral administration. There is no known antidote, according to Marme (*105*). Rabuteau (*124*) showed in 1874 that the muscles would not respond to stimuli after death from thallium. Curci's (*55*) experiments revealed that circulation and respiration were both depressed in frogs; in warm-blooded animals, weakness and collapse were produced, the pulse was slowed, and the blood pressure increased.

Kobert (*93*) reports Luck's experiments (*100*) in which the flesh of a hen poisoned by thallium was fed to 11 rats, all of which died. Cats fed the same vomited, but survived. Spitzer (*139*) killed rats in four days by the application of a paste containing 5 per cent of thallium; a 20 per cent salve killed in two days. Local applications did not cause loss of hair. Cataracts were produced in these animals.

An intensive study of the action of thallous acetate, nitrate, and sulphate was reported by Swain and Bateman (*141*) in 1909. The thallous salts were prepared directly from metallic thallium, and all thallic compounds removed. All results are reported in terms of the metal thallium, regardless of the salt actually injected. The lethal dose of thallium as the acetate injected directly into the lymph sac of the back of 300-gram toads was approximately 16.7 milligrams per kilogram of body weight. Death from respiratory failure followed loss of control of the hind legs.

A toadfish (Porichthys) weighing between 30 and 50 grams died within 50 hours in a 1:2,500 solution of thallium as the chloride (400 milligrams per liter) after exhibiting signs of respiratory distress. Another toadfish died in 53 hours, after two days' contact with the same solution. A concentration of 800 milligrams per liter caused death in 20 hours. A rock cod (Cottidae) died from respiratory distress in a few hours in a solution containing 400 milligrams of thallium per liter. Injection of a solution into the lymphatic trunk just behind the lateral fin was then attempted. A "blue cod" (*Ophiodon elongatus*) died the next day after 20 milligrams per kilogram; a bluefish (Sebastodes) died in four days after 10 milligrams per kilogram, and another in three days after 16 milligrams per kilogram.

Subcutaneous injections of 20 and of 45 milligrams of thallium as the nitrate killed rats in 2 days; 15 milligrams killed two guinea pigs in 5 days; 20 milligrams killed a rabbit in 4 days and another in 6 days, and 40 milligrams in 4 days. Unfortunately, however, the body weights of the animals are not reported, so that calculations of results in the customary terms of milligrams per kilogram can not be made. A dog received 100 milligrams subcutaneously (11 milligrams per kilogram), which caused posterior paralysis and loss of appetite for 10 days, although the animal survived.

TABLE 1.—*Toxicity of thallous salts administered orally to dogs, as determined by Swain and Bateman (141)*

| Salt used | Days until death, after doses (in milligrams per kilo of body weight) were given of— | | | | | |
|---|---|---|---|---|---|---|
| | 13 | 17 | 19 | 20 | 26 | 45 |
| Thallous acetate ($TlC_2H_3O_2$) | 8 | | 9, 15 | | | |
| Thallous nitrate ($TlNO_3$) | | 15 | | 7 | | 4 |
| Thallous sulphate ($Tl_2SO_4$) | | | | | 12 | |

Oral administration to dogs gave the results listed in Table 1. The minimum lethal dose can not be determined from these data, since all test animals died, but it appears to be less than 13 milligrams per kilo.

The authors conclude that thallium is more toxic than lead, being about as potent as arsenic. The administration of 200 milligrams to a dog over a period of 13 days produced the same effect as when administered in 4 days, from which the authors conclude that there is no tolerance for thallium, but a cumulation of action.

The first symptom noted by Swain and Bateman after administration of thallium was lack of coordination in locomotion, localized in the hind legs of the quadrupeds. Trembling, great dilatation of the pupils, emesis, congestion of the gastrointestinal tract, increasing albuminuria, increased urinary volume, and alopecia were noted in most animals; dogs also showed a marked increase in the flow of tears and of bile. A blue line appeared upon the gum margins. Finally respiratory distress developed to cause death by asphyxia. There was no indication of heart failure, toads' hearts continuing to beat for some time after the respiration ceased. Some lesions of the kidneys were noted after 200 milligrams (17 milligrams per kilo) were given, but they were not considered sufficiently severe to cause death, and the suggestion is offered that thallium may favor the production of uremic poisoning. Nephritis was established.

Herfs (*5*, *86*) in 1924 lauded thallium highly; he claimed that 70 milligrams of thallium per kilo killed rats in 2 days and that smaller doses killed in 8 to 14 days, by action upon the central nervous system. House mice were killed by 2 or 3 grains of thallium-treated wheat; 10 mice consumed 262 of 400 kernels of normal wheat and 304 of 400 treated kernels. Cataract was not observed.

In perfusing isolated frog hearts by the Straub method, 0.03 to 0.05 milligram of thallium sulphate caused stoppage of the heart in diastole in 10 to 15 minutes (*23*). The action was antagonized by the addition of calcium to the perfusion solution. Retardation of growth of rats and other warm-blooded animals by thallium is due to disturbances of the calcium metabolism (*21*, *33*, *35*, *37*). Because of these disturbances, conditions resembling rickets are produced, with a progressive failure of the body tissues to store calcium. Histological examinations of the skeletal bones showed definite evidence of rickets (*35*, *37*).

In a further series of papers (*13*, *14*, *15*, *16*, *17*, *18*, *19*, *20*, *22*, *25*, *26*, *27*, *28*, *29*, *31*, *32*, *34*, *38*, *39*, *40*, *41*, *43*, *45*, *78*), Buschke and coworkers showed that thallium poisoning was developed through its actions upon various endocrine glands. This accounts for the failure of tadpoles to grow in very dilute solutions of thallium salts. The action is specifically exerted upon the ovaries or testicles, which may completely atrophy; in a number of rats, complete loss of the testicles was produced; in others no spermatozoa could be found. The epinephrine content of the suprarenal glands was greatly decreased. Involvements of the thyroid gland were also found. Evidence regarding the effect upon the pituitary gland was not so definite, although some involvement seemed demonstrable. Cataracts were produced in rats (*78*) and also proliferation of the mucosa of the cardiac end of the stomach.

Dal Collo (*48*, *49*) confirmed the endocrine action of thallium upon rabbits. Six rabbits weighing 2,500 to 2,800 grams were given 10 milligrams of thallium acetate intravenously the first day, and the daily dose increased 10 milligrams until death supervened on the fifth or sixth day. Guinea pigs were given 1 milligram subcutaneously the first day, and the dose increased by 0.5 milligram a day until death, on the thirteenth to sixteenth day. Rats were fed 1 milligram daily in their food. All animals showed parenchymatous and vascular nephritis, with characteristic epithelial lesions, and diffuse changes in the convoluted tubules.

Transitory hyperglycemia, followed by constant hypoglycemia; sexual changes, but no congenital eye lesions or lesions of the bones or parathyroid gland; leucocytosis; and erythropenia were observed in rats following the administration of thallium salts. No relation or interdependence could be established between alopecia, hypertrophic processes, bone lesions, and the appearence of cataracts by Mamoli (*103*, *104*) in 1926.

Olivier (*113*) observed that long feeding of small doses of thallium to rats caused inflammatory proliferations of the mucosa of the esophagus and cardiac end of the stomach. Ehrhardt (*69*) went a step further in the study of the action of thallium upon the newborn; a female rat was fed large doses of thallium for four days, after which she died. The nursing young were at once transferred to a normal lactating rat and fed her milk, but all showed the typical effects of thallium poisoning. This clearly demonstrates the harmful action of thallium upon the young, whether the transference occurs in utero or in the milk.

Buschke and Peiser (*38*) experimented with an organic thallium compound, thallium dimethyl bromide. The lethal dose to mice was found to be 5 to 6 milligrams per mouse, or 10 times the lethal dose of thallium acetate. Similar symptoms were produced. The hydrogen-ion concentration of thallium solution influenced the rate of amphibian metamorphosis (*7*). The pathological changes produced in various animals by thallium have been investigated by various workers (*51, 85, 95, 102, 110, 134*). Popenoe (*121*) suggested the use of thallium as an ant poison.

#### PRODUCTION OF ALOPECIA (LOSS OF HAIR)

Several investigations have been made to determine the nature of thallium action in the production of alopecia (*8, 61, 70, 71, 145, 143*). In 1898, Hallopeau (*83*) rubbed a salve containing thallium acetate upon the back of a guinea pig; the pig died but the hair was unaffected. In 1900, Buschke (*13*) observed that the feeding of very small quantities of thallium to rats produced alopecia, and had a cumulative action. In a subsequent report (*14*), he noted that thallium acetate or carbonate produced alopecia in mice, rats, and monkeys; in rats it had a central action, since the diaphoretic action of pilocarpine was not altered. The series of papers by Buschke and coworkers clearly demonstrated that thallium action was exerted upon the sympathetic nervous system. The hairs of the scalp and chest, under the control of the autonomic nervous system, were loosened readily by thallium; the hairs of the eyebrows and lashes, and those upon the abdomen not under the control of the autonomic system were unaffected. One-tenth of a milligram of thallium acetate fed rats daily produced alopecia (*39*). Other workers also showed that the hairs upon the scalp and abdomen were most readily removed; lanugo and abdominal hairs with more difficulty; hairs at the nose and snout not affected. The local application of thallium did not cause loss of hair. A 5 per cent thallium acetate salve killed rats in four days; 20 per cent in two days; more rapid deaths were not produced (*113, 139*).

Dixon (*62*) reported a very thorough study of the mechanism of depilation by thallium. He found that no other substance has a similar action in producing alopecia; that thallium has this action upon all animals with the possible exception of the guinea pig. The hair at first becomes less glossy, then is easily rubbed off after about seven days. After 14 days it is easily shed, practically all hair being out by the nineteenth day. Alopecia begins at the nape of the neck and around the ears; hairs from the chin and the nose are the last to be lost. The new growth of hair starts in about the fourth week, and is completed by the end of the second month. Local applications of thallium did not cause depilation or affect the blood vessels. Interruption of growth of the hair was due to failure of transition of the large polygonal cells to stratified cells of the hair. Very large doses caused degeneration of the hair follicles. Thallium was found to increase selectively the reactivity of the entire autonomic nervous system, just as strychnine increased the activity of the spinal cord. Thallium was excreted in the urine, but did not appear to injure the kidneys or to cause albuminuria. Spectroscopically it was found in practically every tissue of the body.

Truffi (*143*) found that rats were more sensitive than guinea pigs, cats, or rabbits. Inunction gave circumscribed depilation, because of action on the hair follicles.

#### ACTION OF THALLIUM SALTS ON MAN

During his original work in 1863, Lamy (*94*) developed general lassitude and pains of the lower limbs, which he attributed to the vapors of thallium. Crookes (*54*), however, stated that he had not been affected by thallium fumes, or by the ingestion of 65 to 130 milligrams of thallium salts. According to Bullard's report (*12*), the ingestion of between 130 and 250 grains (of thallium acetate?) during a week produced diarrhea, muscular weakness, and tenderness over the nerve trunks. Since, however, both lead and arsenic were found in the urine in this case, this result should not be ascribed to thallium alone.

Olmer and Tian report a case in 1908 (*114*) in which the application of a thallium-acetate salve to the chest and thorax of a 27-year-old man produced violent pains, especially in the extremities, which were increased by pressure on the peripheral nerves; diffuse alopecia; persistent albuminuria; stomatitis; and general depression. These symptoms continued for about a month before remission. The cerebrospinal fluid collected 25 days after application of the paste showed upon spectroscopic examination the presence of 0.02 milligram of thallium per liter.

Buschke, Peiser, and Klopstock (*42*) relate that a 34-year-old printer attempted suicide by taking 750 milligrams of thallium nitrate (10 milligrams per kilo) by mouth. Marked pains in the feet and limbs, emesis, and achlorhydria were followed by alopecia in 3 weeks. New hair returned in 8 weeks, but 11 weeks were required for the return of normal gastric acidity. Slow elimination of thallium was also noted in two children.

Lührig (*101*) gives an account of a 2-year-old child who ate an undetermined quantity of a thallium paste smeared upon bread and exposed as a rat poison. Rapid collapse and vomiting were checked temporarily by injections of glucose, but a relapse followed, and the child died in 29 hours. Post-mortem examination showed nothing abnormal except marked irritation of the stomach and small intestines. Spectroscopic examination revealed the presence of thallium in various tissues. A 4-year-old child ate some of the same poisoned bait, but apparently in smaller quantities, as he survived.

Brieger (*11*) reports the death of a child in 1927 following the consumption of an undetermined quantity of thallium-coated grain, which had been mixed with grain treated with strychnine. Strychnine-poisoning symptoms were produced. After death the presence of both thallium and strychnine was demonstrated in the viscera. The death of children or of adults following the consumption of thallium-treated grain or thallium paste exposed as a rat poison has been reported only too frequently (*4*, *42*, *76*, *82*, *99*, *126*). Althoff (*4*) reported seven cases of poisoning in one family. Fridli (*76*) determined thallium by titration with potassium iodide. In a case in which 2.5 grams of thallium acetate had been taken by mouth, 5 milligrams of thallium were found in 100 grams of urine; 1.6 milligrams in 100 grams of kidney; and 3.3 milligrams in 100 grams of liver. The greater part had already been eliminated in the urine.

A recent case of poisoning by the administration of thallium acetate has attracted much comment (*3*, *91*, *135*). Through a mistake in conversion from the metric to the apothecaries' system, 85 milligrams of thallium acetate per kilo were administered instead of 8.5

milligrams per kilo. Three boys receiving this dose died after several days.

Pharmacological and toxicological studies of thallium (*77*, *81*, *115*, *128*, *129*) have been made during the past few years.

Swelling of the gums, the development of a blue line at the junction with the teeth (*122*); general muscular atrophy, especially of the jaw and spine; cardiac depression (*127*); and cardiac lesions (*106*); hypochlorhydria or achlorhydria (*64*, *75*); disturbances in calcium metabolism (*44*); severe injury to the thyroid gland (*56*, *64*); pains in the legs and sciatic nerves after 300 to 500 milligrams of thallium acetate to adults (*79*) or children (*118*); and eosinophilia and leucocytosis (*75*) have been recorded following the ingestion of thallium medicinally. Blyth (*10*) recorded the elimination of thallium in the tears, milk, and urine; he, as well as Fasani (*71*), stated that the same symptoms are produced in man as in animals, and that poisoning occurs through action on the nervous system.

Kaps (*90*) gives a good summary of the symptoms produced in criminal (fatal) subacute thallium poisoning: (1) A short period of excessive gastrointestinal pain, emesis, nausea, colic, and diarrhea, which soon changes to obstinate constipation; (2) disorders of the central and vegetative nervous system—conjunctivitis, blepharitis, alopecia totalis, acute suppurative dermatitis of the face, acroparesthesias, sensitiveness of the muscles and joints, which increases upon pressure, retrobulbar neuritis, amaurosis, and a decline of the psychic functions to complete dementia; and (3) degeneration of the heart, liver, and kidneys. The mechanism of thallium poisoning following subcutaneous injection must be sought in the action upon the central and vegetative nervous systems, with secondary disturbances of the nervous regulation of the endocrine glands. In a survey of industrial poisonings among thallium workers, Meyer (*109*) and Teleky (*142*) report reduction of vision, cataract, and nephritis. Among the principal symptoms noted were pains in the legs, loss of hair, disturbances of sensation and the sympathetic nervous system; endocrine involvements of various sorts; and lymphocytosis, which increased after work was stopped.

## MEDICINAL USES

### FOR COLLIQUATIVE SWEATS OF PHTHISIS

To check the night sweats of phthisis, Combemale (*50*) in 1898 recommended a dose of 100 milligrams of thallium acetate at bedtime for not to exceed four successive nights. Its value was reaffirmed by Huchard (*86*) and by Buschke (*15*). Three subsequent papers, however, were published in 1898 stressing the danger of such medication. Vassaux (*144*) recorded marked pain in the calves of the legs and in the peripheral nerves after doses of 100 and 200 milligrams of thallium acetate. Dubreilh (*68*) obtained alopecia. Jeanselme (*88*) administered 30 milligrams of thallium acetate three times a day for three days (a total of 270 milligrams), which decreased the sweating but produced pains in the abdomen and legs; after two weeks, profuse alopecia with permanent injury to some of the hair follicles resulted. Chemical analysis of the hair failed to show the presence of thallium. Because of its toxicity thallium is not used for this purpose in present-day medical practice.

### AS A DEPILATORY

Thallium preparations have been used more or less empirically to remove hair in the treatment of alopecia areata and of ringworm. It is not certain who introduced this method of treatment. Olmer and Tian's (*114*) patient developed profuse diffuse alopecia after the application of a thallium paste to the chest. Sabouraud (*130*) recommended an ointment containing 1 per cent of thallium acetate as a depilatory, but stated that quantities in excess of 300 milligrams of the salt produced toxic effects. Pöhlmann (*120*) confirmed the central action of thallium in producing alopecia, and showed spectroscopically that it was eliminated by the kidneys. A symposium of the toxic effects of thallium was reported in Spain with the conclusion that the acetate was more potent than the sulphate (*132*). Buschke and Peiser (*31*) and Sabouraud (*130*) recommended the use of 3 grams of a 1 per cent salve of thallium salt as a depilatory.

Clinical reports of the use of thallium salts, more especially as depilatories, have been given in the literature of many countries (*1, 2, 6, 47, 56, 59, 65, 74, 96, 97, 98, 112, 116, 118, 119, 127, 143, 148*). The present status of thallium therapy is well summarized in a "Miscellany" report in the Journal of the American Medical Association (*1*) and in a subsequent editorial in the British Medical Journal in 1929 (*2*). Apparently thallium was used systematically in Mexico in 1918 on account of the shortage in X-ray tubes (*2*). Cicero (*47*) found that 5 milligrams per kilo was too small a dose for satisfactory results and used 8 milligrams per kilo without serious complications.

Thallium was not so favorably received in England, perhaps on account of the lack of success in the treatment of the particular ringworm that occurred there. The doses, reactions, and cures in this series of clinical reports are given in Table 2. Thallium acetate was used in each instance.

Careful attention must be given to body weight and doses: Eight milligrams per kilo are necessary for successful depilation, smaller doses being only partially effective. Serious reactions have followed doses as small as 4 milligrams per kilo; adults are much more susceptible than children, as 8 milligrams per kilo have been toxic. The maximal dose for any patient should not exceed 300 milligrams, irrespective of the body weight. Special attention is called to the contra-indication of thallium in any cases of albuminuria or kidney involvement. Treatment should not be repeated until all the thallium from the preceding course of medication has been eliminated (two to three months). It is also emphasized that these treatments should be under the care and observation of a physician.

TABLE 2.—*Clinical response to thallium in treatment of ringworm*

| Reference | Dose per kilogram of body weight | Patients' ages | Patients | | | Remarks |
|---|---|---|---|---|---|---|
| | | | Treated | Poisoned | Ringworm cured | |
| | *Milligram* | *Years* | *Number* | *Number* | *Number* | |
| Davies (*67*) | 4, 5, 6 | 12, 14, 35 | 3 | 3 | | |
| Drummond (*67*) | 5 | | 4 | | 4 | |
| Peters (*118*) | 5 | | 500 | | | Mexican schools |
| Davies and Andrews (*68*) | 7.5 | 8 | 1 | 1 | | |
| | 8.5 | 11 | 1 | 1 | | |
| Devane (*60*) | 8 | | 45 | | | |
| Seaston and Wilson (*136*) | 8 | | 30 | | | Old solution. |
| | 8 | | 50 | 5 | 47 | Fresh solution. |
| Buschke and Langer (*27*) | 8 | | 100 | | | Berlin hospital. |
| Felden (*72*) | 8 | | 47 | | 36 | |
| Peyri (*119*) | 8–9 | | 74 | 10 | 52 | |
| Dowling and Kelman (*64, 65*) | 8.5–9 | | 90 | 78 | | |
| | 8.5–9 | Less than 3 | 16 | | 16 | |
| | 8.5–9 | More than 3 | 46 | | 35 | |

Sollmann (*138*) concludes: "The therapeutic use (of thallium) has repeatedly caused severe poisoning and is scarcely justified."

#### ANTIDOTES FOR THALLIUM POISONING

No general antidote is known for thallium poisoning. Prompt use of the stomach tube and the induction of vomiting to remove any unabsorbed material in the stomach are indicated. As the iodide and chloride are less soluble than other thallium salts, potassium iodide or sodium chloride may be given, followed by gastric lavage or vomiting. The intravenous injection of sodium thiosulphate (*38*) gave indifferent results. Removal from exposure for several months should be adequate in cases of chronic poisoning.

## LABORATORY EXPERIMENTS

#### METHOD ADOPTED FOR FEEDING EXPERIMENTS

It was found that thallium salts fed in ordinary food were very toxic to rats (*111*). In order to compare the toxicity with that of other rat poisons, a similar method of feeding became necessary. Some investigators dissolved the test substance in the animals' drinking water, but this method appeared too inaccurate for use in the work here reported upon. Other investigators have dissolved weighed quantities of a test substance in a known volume of water or other solvents and mixed the solution with weighed bulks of food, or administered the solution by pipette directly into the mouths of test animals. These methods appeared very cumbersome, even though somewhat more accurate in dosage.

Experience in the feeding of other poisons to rats led to the adoption of the following method of preparation of the poisoned bait: The ordinary laboratory rat food was screened, and that portion passing through a 20-mesh sieve (a sieve with 20 meshes to the linear inch, or 400 apertures to the square inch) used as a vehicle. Success in the use of this method is dependent upon the care used in finely pulverizing the poison and thoroughly mixing with a finely screened bait. The sample of thallium compound to be tested was powdered, accurately weighed, thoroughly mixed with a weighed quantity of the sieved rat food by a spatula, and finally passed through a 20-mesh sieve several times to insure thorough mixing. Concentrations were prepared upon the basis of the actual thallium content, regardless of the salt fed. The thallium concentration in the finished baits ranged from 0.25 to 10 per cent, although 0.5 per cent was commonly used.

In an effort to standardize the condition of the rats used in these tests, all animals (wild or white) were kept under laboratory conditions for several days to a month, and fed ordinary laboratory rat food. They were then placed in individual cages and deprived of food for 12 to 24 hours to insure uniformly empty stomachs and good appetites. Water was offered at all times. The rats were carefully weighed at the end of the deprivation period, and doses of thallium were calculated in terms of milligrams of thallium per kilogram of body weight of animals. The determined quantities of bait were accurately weighed and placed in large glass sponge cups, which were introduced into the cages at a stated time. Frequent inspections were made, and the rapidity with which the different baits were attacked and consumed was noted. The sponge cup, containing any uneaten food, was removed after several hours, and the remaining quantity weighed, to determine the quantity of thallium consumed. On the next day, all animals were returned to the regular rat diet, with plenty of water. In general, the animals were kept in individual cages for a period of five days. All animals dying within five days (occasionally it took a longer time) that showed symptoms of thallium poisoning were recorded as dying from the dose consumed. The development of toxic symptoms or death was watched; in some instances post-mortem examinations were made to determine the gross changes produced by the poison.

The minimum lethal dose was taken as the quantity of thallium that caused the death of all test animals, or practically all, within the period of five days. Doses somewhat larger than the accepted minimum lethal dose must kill all test animals; doses somewhat smaller (20 to 25 per cent) killed less than half of the test animals. The minimum lethal dose is considered to be accurate within 10 to 20 per cent, which is the usual range of reaction of test animals.

## FEEDING EXPERIMENTS

### SERIES 1: COMMERCIAL THALLIUM-TREATED GRAIN

A sample of grain and one of a paste containing thallium as the toxic ingredient were tested in July, 1924. The grain appeared to be medium-sized kernels of wheat coated with a reddish scum. The paste was of a greenish hue and had the consistency of lard. Chemical analyses of these products were not undertaken, as analytical methods were not readily available. Count of the grain showed that 440 kernels weighed 17.5 grams and that 680 kernels weighed 27.0 grams, or an average of 25 kernels to the gram.

Seven wild rats, weighing 78 to 335 grams, were offered weighed and counted quantities of the grain at 3.30 p. m., July 25, 1924. The uneaten food was removed at 9 a. m. the next morning. All animals were alive on the second day; on the third day after feeding, all but one died, and the survivor died during the night. Body weights and other pertinent data are tabulated for convenient reference in Table 3. The quantity of food eaten varied from 0.35 to

TABLE 3.—*Toxicity of commercial thallium-treated grain to rats*

| Body weight of rats (grams) | Grain offered | | Grain eaten | | | Days until death |
|---|---|---|---|---|---|---|
| | Kernels | Weight | Weight | Per cent | Grams per kilo of body weight | |
| WILD RATS | | | | | | |
| | *Number* | *Grams* | *Grams* | | | |
| 78 | 16 | 0.5 | 0.35 | 70 | 4.50 | 3 |
| 335 | 27 | 1.0 | 1.0 | 100 | 3.00 | 3 |
| 230 | 24 | 1.0 | 1.0 | 100 | 4.35 | 4 |
| 200 | 66 | 2.5 | 0.75 | 30 | 3.75 | 3 |
| 325 | 63 | 2.5 | 2.5 | 100 | 7.70 | 3 |
| 80 | 116 | 5.0 | 0.6 | 12 | 7.50 | 3 |
| 80 | 128 | 5.0 | 0.6 | 12 | 7.50 | 3 |
| WHITE RATS | | | | | | |
| 195 | 12 | 0.5 | 0.5 | 100 | 2.55 | 4 |
| 175 | 12 | 0.5 | 0.5 | 100 | 2.85 | 4 |
| 157 | 13 | 0.5 | 0.5 | 100 | 3.20 | 2 |
| 210 | 26 | 1.0 | 1.0 | 100 | 4.75 | 3 |
| 182 | 25 | 1.0 | 1.0 | 100 | 5.50 | 3 |
| 175 | 26 | 1.0 | 1.0 | 100 | 5.70 | 3 |
| 210 | 63 | 2.5 | 2.5 | 100 | 11.90 | 3 |
| 175 | 64 | 2.5 | 2.5 | 100 | 14.30 | 3 |
| 160 | 58 | 2.5 | 2.5 | 100 | 15.65 | 3 |
| 210 | 125 | 5.0 | 4.0 | 80 | 19.05 | 3 |
| 175 | 127 | 5.0 | 4.15 | 83 | 23.70 | 3 |
| 175 | 130 | 5.0 | 4.75 | 95 | 27.15 | 3 |

2.5 grams, larger rats consuming the larger quantities. One gram of poisoned grain per rat killed two large rats. The minimum lethal dose was not determined, since all the test animals died, but evidently it is less than 3 grams of treated grain per kilogram of body weight (roughly equivalent to 30 treated kernels per pound of rat). Deaths occurred on the third and fourth days, even with very large doses of bait, which shows that thallium is a slowly acting poison to rats.

Twelve white rats, weighing between 157 and 210 grams, were offered weighed and counted quantities of the grain at 12.15 p. m. on August 9, 1924. All uneaten food was removed at 9 a. m. on August 11, when all rats were found to be alive and in good condition. One rat died the second day, the remainder on the third or fourth day, as shown in Table 3. A larger quantity of food was consumed by the white rats than by the wild rats, but over a longer period of time. During the same time interval, food consumption appeared to be about the same by the two varieties. No relationship was found between the quantity of poisoned grain eaten and the time until death; the earliest death occurred in a rat that had eaten 3.2 grams of grain per kilo, while others that had eaten five to eight times as much died a short time later. Thallium does not appear to kill rats rapidly, regardless of the doses consumed. Since all animals died, it is not possible to determine the minimum lethal dose from these data, except that it appeared to be less than 2.5 grams of grain per kilo of body weight. No significance should be attached to the fact that white rats died from somewhat less than the smallest dose killing wild rats, as an insufficient number of animals were used to confirm this difference.

Three white rats, weighing 190, 205, and 212 grams, respectively, were fed a mixture of 7.5 grams of paste and 7.5 grams of rat biscuit on July 25, 1924. All animals were in the same cage. Some of the paste was uneaten after 12 hours. The heaviest rat died on the third day; the other two showed extensive diarrhea and died during the night.

On August 9, 1924, approximately 1 gram of paste was smeared on the back, between the shoulders, of each of six white rats. The rats were then placed in individual cages to prevent them from licking poison from the backs of one another. Two days later, decided reddening of the noses of four was noted. On the fourth day three rats died, and the next day the other three died. Post-mortem examinations failed to show any abnormalities.

This preliminary series of feeding experiments with the thallium grain and paste showed that wild and white rats died about three days after the consumption of comparatively small quantities of poisoned food. A series of experiments was then performed with chemically pure thallium compounds, to determine the nature of their action and the minimum lethal dose.

### SERIES 2: CHEMICALLY PURE THALLIUM SULPHATE

A sample of chemically pure thallium sulphate was pulverized in a mortar and thoroughly mixed with screened rat food. Since thallium sulphate has the formula $Tl_2SO_4$ and contains 81 per cent of thallium, 1.24 grams of thallium sulphate were taken as the equivalent of 1 gram of thallium.

Seventy-two white rats, weighing between 103 and 197 grams, were fed specified doses of thallium as sulphate, December 4 to 17, 1924. Poisoned baits were consumed with the same eagerness as control food containing no thallium. In most instances all food was consumed within 15 to 30 minutes after exposure. The results obtained in this series of experiments are reported in Table 4. Twenty-five milligrams of thallium per kilo of body weight of rats (equivalent to 31 milligrams of thallium sulphate per kilo) killed 73 per cent of the rats tested. All doses of 35 milligrams per kilo or larger, or an increase of 40 per cent in dosage, killed all rats. A dose of 20 milligrams per kilo, or a decrease of 20 per cent in dosage, killed about a third of the rats tested. Accordingly, 25 milligrams per kilo was selected as the minimum lethal dose. Confirmation of this value was obtained in another series of feeding experiments on May 9, 1927. Fifteen rats weighing 125 to 175 grams were fed thallium baits. (Table 4.) With a minimum lethal dose of 25 milligrams of thallium per kilo when fed to rats, thallium proves to be more toxic than any of the ordinary rat poisons except strychnine.

TABLE 4.—*Toxicity of thallium as sulphate to white rats, 1924 and 1927*

EXPERIMENTS IN 1924

| Dose of thallium per kilogram of body weight | Rats fed | Number of rats dying after— | | | | | Total deaths | |
|---|---|---|---|---|---|---|---|---|
| | | 1 day | 2 days | 3 days | 4 days | 5 days | | |
| *Mg.* | *Number* | | | | | | *Number* | *Per cent* |
| 10 | 10 | ------- | ------- | ------- | ------- | ------- | 0 | 0 |
| 15 | 8 | ------- | 1 | ------- | ------- | ------- | 1 | 12 |
| 20 | 8 | ------- | 2 | 1 | ------- | ------- | 3 | 37 |
| 25 | 11 | ------- | 1 | 2 | 4 | 1 | 8 | 73 |
| 35 | 5 | ------- | 3 | 2 | ------- | ------- | 5 | 100 |
| 50 | 5 | ------- | ------- | 1 | 2 | 2 | 5 | 100 |
| 75 | 5 | ------- | ------- | 3 | 2 | ------- | 5 | 100 |
| 100 | 5 | ------- | 3 | 2 | ------- | ------- | 5 | 100 |
| 200 | 5 | 1 | 4 | ------- | ------- | ------- | 5 | 100 |
| 500 | 5 | 2 | 3 | ------- | ------- | ------- | 5 | 100 |
| 1,000 | 5 | 4 | 1 | ------- | ------- | ------- | 5 | 100 |

EXPERIMENTS IN 1927

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 20 | 5 | ------- | ------- | 1 | 2 | ------- | 3 | 60 |
| 25 | 5 | ------- | ------- | 1 | 4 | ------- | 5 | 100 |
| 30 | 5 | ------- | ------- | ------- | 5 | ------- | 5 | 100 |

It was noted that death usually occurred on the second or third day after feeding thallium bait, unless the quantity of poison taken was excessive. Ten times the lethal dose killed only one out of five rats within one day; 40 times the lethal dose killed only four out of five rats within one day. This would indicate that thallium must be absorbed from the gastrointestinal tract and localized within the tissues before producing death. For rats, at least, thallium is a definite poison, but not a rapid one.

Results obtained with the thallium-treated grain in series 1 suggested that the minimum lethal dose of the grain was 2.5 grams per kilo, or possibly somewhat less. Results obtained in series 2 showed that the minimum lethal dose of thallium as sulphate is 25 milligrams per kilo. Accordingly, it would appear that the grain fed contained 25 milligrams of thallium on 2.5 grams of grain, or 1 per cent of thallium. This has not been confirmed chemically. The exact lethal dose of the grain was not determined; it is conceivable that it might be lower than 2.5 grams per kilo, which would proportionately increase the thallium content. It appears safe to conclude, however, that the thallium-treated grain as fed contained at least 1 per cent of thallium.

#### SERIES 3: COMMERCIAL THALLIUM PREPARATIONS

Commercial supplies of thallium compounds were obtained by the Bureau of Biological Survey for use in controlling prairie dogs and ground squirrels in the West where strychnine baits had been refused by the rodents. It was soon found that some particular shipments of thallium products were rejected when mixed with the usual baits, although other lots were taken readily and effectively. A set of six samples was transmitted for examination and analysis on November 25, 1927, representing acceptable and nonacceptable material employed by E. E. Horn, of the Biological Survey. His descriptions of these samples show the degree of success obtained in using them under field conditions:

*Sample No. 1.*—Taken from supply furnished during November, 1926. This material was absolutely refused when applied on steam-crushed oats at Flagstaff, Ariz., early in May, 1927. It was but slowly eaten at the Vallecito Ranger Station, Colorado (La Plata County, Zuni prairie dogs). It was slowly accepted by the Gunnison prairie dogs in Moreno Valley, N. Mex., during July, 1927, and was refused by Plains prairie dogs at Tatum, Lea County, N. Mex., during August, 1927. The trials at Tatum were under conditions of extreme summer heat. Acceptance in Moreno Valley, N. Mex., was slower than in a supply obtained by A. E. Gray and used during July, August, and September of the same year.

*Sample No. 2.*—From a supply furnished in April, 1926. During the spring of 1926 at Flagstaff, Ariz., this material was readily accepted and gave excellent results in controlling Zuni prairie dogs. In the spring of 1927 it was refused at Flagstaff, at Vallecito Ranger Station (Zuni prairie dogs), and in the Moreno Valley (Gunnison prairie dogs). In the summer of 1926 the material was a pure gray white, but in 1927 many yellowish flakes were noticeable in the product. This material was recieved and kept in a tin container.

*Sample No. 3.*—From a small supply received by the laboratory from S. E. Piper in California during September, 1927. No information is available here as to the source, but it is labeled "Thallium Sulphate—German production—thallium sulphate 99 per cent, inert material 15." This sample was received too late to be used for field tests of acceptability. Earlier German products were highly acceptable and of uniform toxic effect.

*Sample No. 4.*—A sample of thallous carbonate received during the late summer of 1926. It was highly acceptable to the Zuni prairie dogs at Flagstaff, Ariz., during August and September, 1926, and was readily taken by Gunnison prairie dogs in the Moreno Valley of New Mexico during a time when some of the sulphate salts were refused. At Tatum, N. Mex., during August, 1927, the carbonate was better accepted than the various sulphate samples, but was of too low acceptability to be of value. (Weather very hot. Extreme drought during part of tests, and summer rains occurring during the latter part of operations.)

*Sample No. 5.*—Thallous sulphate furnished to the Arizona district during the summer of 1926. This material was held over and used for the first time in the spring of 1927. Under prevailing spring winds refusal resulted. D. A. Gilchrist noted and reported an offensive odor in the material. This was removed by the American Smelting and Refining Co. chemists by heating to 150° C. for 30 minutes and placing in glass containers. After the spring winds subsided all baits were accepted with avidity.

*Sample No. 6.*—This sample has not been tried out in field operations but an analysis and feeding test are desired of it in order to ascertain its chemical purity, which would serve as a guide in possible future purchases of thallium sulphate.

Samples 1, 2, 4, and 5 came from one American manufacturer; sample 6 from another. Unsuccessful attempts were made to arrange for chemical analyses of these samples. Pressure of other work prevented feeding experiments until April 10, 1928, when doses of 20 and 40 milligrams of each sample were fed to three rats each. The rats ranged in weight from 145 to 355 grams. All baits were prepared to contain 0.5 per cent of thallium salt (0.4 per cent of thallium). Observations were continued over seven days, during which time all the rats died. (Table 5.) This prevents the accurate determination of the lethal doses of the respective samples. The fact, however, that all rats fed 20 milligrams per kilo died does prove that these samples were as toxic as the chemically pure thallium sulphate used in series 2.

TABLE 5.—*The toxicity of commercial thallium compounds to white rats*

| Sample No. | Acceptance | Rats fed | Number of rats dying after period stated when fed 20 milligrams per kilo | | | | | | | Rats fed | Number of rats dying after period stated when fed 40 milligrams per kilo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 day | 2 days | 3 days | 4 days | 5 days | 6 days | 7 days | | 1 day | 2 days | 3 days | 4 days |
| | | *Number* | | | | | | | | *Number* | | | | |
| 1 | Poor | 3 | | | 1 | 1 | | | 1 | 3 | | | 2 | 1 |
| 2 | do | 3 | | | 1 | 1 | | | 1 | 3 | | | 3 | |
| 3 | Unknown | 3 | | | | 1 | | 2 | | 3 | | | 2 | 1 |
| 4 | Low | 3 | | 1 | 1 | 1 | | | | 3 | | | 2 | 1 |
| 5 | Ready | 3 | | | 2 | 1 | | | | 3 | | | 3 | |
| 6 | Unknown | 3 | | 1 | 2 | | | | | 3 | | 1 | | 2 |

Of the 18 rats fed 20 milligrams per kilo, 14 consumed all their food within 15 to 20 minutes, 2 in about an hour, and the other 2 during the night. Of the 18 fed 40 milligrams per kilo, 12 finished eating within 15 to 20 minutes, 3 within an hour, and 3 during the night. No differences were noted in the acceptance of sample 1, which had a poor field acceptance, and of sample 5, which was readily taken in the field. Time until death was somewhat longer in this series than in the preceding tests, but too few animals were used to regard this as significant. Sample No. 6, an American product, appeared to kill as rapidly if not more so than the German sample, No. 3.

These feeding experiments failed to reveal any differences in acceptability or toxicity in the six samples studied. Further intensive feeding experiments would be needed upon several hundred rats to determine whether significant differences in time between feeding and death might be expected. It may be that rats are less susceptible to foreign odors or tastes than are prairie dogs, when poisoned baits are offered them; or the nature of the bait with which the poisons are mixed may be a contributing factor in the acceptance or rejection of specific lots of poisoned baits.

### PHYSIOLOGICAL ACTION ON RATS

Rats appeared restless and uneasy 24 hours after the consumption of a fatal dose of thallium. Loss in appetite usually occurred, followed by respiratory distress, labored breathing, and death by respiratory failure. Post-mortem, the heart was engorged; the lungs and liver usually congested, and in some cases the kidneys and spleen; the stomach lining was hemorrhagic. Alopecia was not observed in the comparatively short time before death; surviving rats showed some losses of hair 10 to 15 days after feeding.

### TOXICITY OF THALLIUM TO RABBITS BY INTRAVENOUS INJECTION

The quantity of thallium as chemically pure thallium sulphate that would kill rabbits was also determined. Aqueous solutions containing 0.5 to 1.0 per cent of thallium (5 to 10 milligrams of thallium per cubic centimeter, or 6.18 to 12.35 milligrams of thallium sulphate per cubic centimeter) were freshly prepared and injected into the marginal ear veins of Belgian hares weighing 1,530 to 2,250 grams. Observations were made from time to time to determine the onset of poisoning symptoms and the occurrence of death. The results obtained are given in Table 6. The minimum lethal dose of thallium, as the sulphate, intravenously injected into rabbits is 25 milligrams per kilo of body weight. Identical results were obtained in the 1924 and 1927 experiments.

TABLE 6.—*Toxicity of thallium to rabbits*

| Body weight | Dose of thallium injected, milligram per kilogram of body weight | Result | Body weight | Dose of thallium injected, milligram per kilogram of body weight | Result |
|---|---|---|---|---|---|
| 2,250 | 10 | Survived. | 1,700 | 50 | Died in 1 day. |
| 1,800 | 25 | Died in 1 day. | 1,750 | 75 | Do. |
| 2,035 | 25 | Died in 2 days. | 1,530 | 100 | Do. |
| 2,220 | 25 | Do. | | | |

## SUMMARY

### LITERATURE

Thallium forms a series of stable, crystalline, water-soluble salts, most important of which are the acetate ($CH_3COO-Tl$) and the sulphate ($Tl_2SO_4$). Quantities as small as 0.002 milligram per liter (2 parts per billion) may be detected by the characteristic green line in the spectrum.

Thallium has a strong oligodynamic action on bacteria.

In acute poisoning in man or animals, marked interference with locomotion, paresis or paralysis of the lower posterior limbs, loss of appetite, decreased gastric acidity, emesis, diarrhea (which rapidly changes to obstinate constipation), a purple-blue line upon the gum margins, albuminuria, nephritis, marked respiratory depression, and death by asphyxia are noted. In general, the heart and circulation are not involved. Post-mortem, effusions of blood into the lungs, marked irritation of the gastrointestinal tract, and inflammatory proliferation of the mucosa of the esophagus and cardiac end of the stomach are recorded.

The lethal dose following administration has not been carefully determined but is approximately 0.5 milligram per mouse, 25 milligrams per kilo of body weight for rats, and 10 to 15 milligrams per kilo for dogs.

In chronic poisoning, reduction of vision, nephritis, pains in the muscles and sciatic nerves, general alopecia, disturbances of the endocrine glands, particularly the ovaries, testicles, thyroid, suprarenal, and pituitary glands, through action upon the central and sympathetic nervous systems, are reported. Cumulative action is established. Disturbances in calcium metabolism are reported to account for rickets and for checking growth. Thallium is slowly eliminated in the tears, milk, and urine, two to three months being required for complete elimination of medicinal doses. Human beings exhibit the same symptoms as animals, alopecia being the most pronounced symptom.

Thallium has been abandoned for treatment of night sweats of phthisis because of its toxicity. Under carefully guarded conditions it may be of value in the production of alopecia in the treatment of ringworm in children, when doses of 8 milligrams per kilo of body weight are given under a physician's direction and observation. Toxic reactions are frequently obtained with a dose of this size or even smaller.

Information in the literature confirms the conclusion of Swain and Bateman (*141*) that "Thallium deserves to be classed among the most toxic of the elements."

## LABORATORY EXPERIMENTS WITH RODENTS

By the standardized method developed for preparing and feeding poisons to rats, about 2.5 grams of a sample of commercial thallium-treated grain per kilo of body weight was found to kill wild and white rats in three to four days. Approximately 1 gram of a paste containing thallium caused death in the same time, when applied to the skin of the back. The minimum lethal dose of chemically pure thallium sulphate was found to be 25 milligrams of thallium, or 31 milligrams of thallium sulphate per kilo, when fed to rats. Death usually occurred on the second or third day. Six commercial thallium preparations were studied; some of them had been refused by prairie dogs in field tests, while other lots had been taken readily. All samples killed rats at 20 milligrams per kilo and were consumed with equal readiness.

Within 24 hours after consuming a fatal dose of thallium, rats became restless and lost their appetite, and difficulties in breathing developed, which terminated in death from respiratory failure. Post-mortem, congestion of the heart, liver, and lungs and sometimes of the kidneys and spleen was noted. Rats surviving sublethal doses of thallium showed alopecia 10 to 15 days after feeding.

Intravenously injected into the marginal ear veins of rabbits, 25 milligrams per kilo of thallium was found to be the minimum lethal dose.

## CONCLUSIONS

Although thallium has been employed in human medicine in doses of 8 milligrams per kilogram of body weight, its use is dangerous and is decreasing.

The minimum lethal dose of thallium, fed as the sulphate to wild or to white rats, is 25 milligrams per kilogram of body weight.

Death usually occurs on the second or third day after feeding and is due to respiratory failure.

Thallium affects the sympathetic nervous system, thereby producing general alopecia (loss of hair), pains in the muscles and nerves of the legs, and disturbances of the endocrine glands (particularly the ovaries and testicles and the thyroid, suprarenal, and pituitary glands). Calcium metabolism is upset and leads to rickets.

Injected intravenously into rabbits, the minimum lethal dose is 25 milligrams per kilogram.

Thallium is among the most toxic substances recommended for rat control; comparative tests with other rat poisons by the same feeding method give the following minimum lethal doses:

| | Mg. per kgm. of body weight |
|---|---|
| Thallium | 25 |
| Strychnine | 20–25 |
| Arsenious oxide | 100 |
| Red-squill powder | 250 |
| Barium carbonate | 750 |

Thallium is a cumulative poison of high toxicity and is without taste, smell, or other warning property. It should not be recommended to the public as a rodent poison. Where the use of thallium is found necessary for the control of highly resistant species of rodents, it should be entrusted only to persons who understand its dangerous qualities and who will exercise appropriate care in handling it.

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U. S. GOVERNMENT PRINTING OFFICE: 1931

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