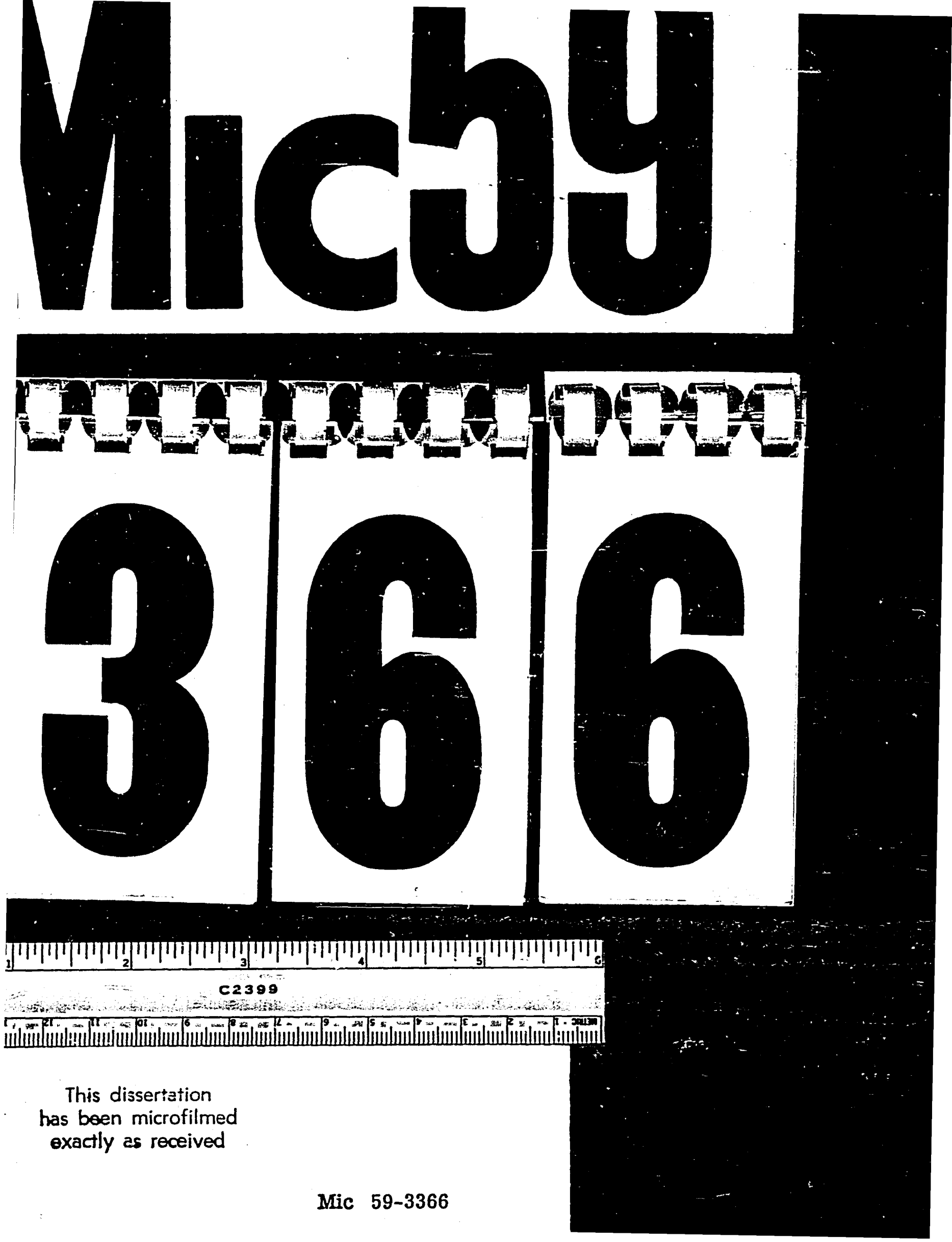

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THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

A STUDY OF THE DISTRIBUTION OF THALLIUM IN TISSUES, BLOOD, URINE AND FECES

A DISSERTATION

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ARNOLD LOUIS PRITSCHOW

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A STUDY OF THE DISTRIBUTION OF THALLIUM IN TISSUES, BLOOD, URINE AND FECES

APPROVED BY

Otto Shoemaker

Paul V. Smith

William Standley

Richard D. Thayne

Arley T. Bever

DISSERTATION COMMITTEE

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A STUDY OF THE DISTRIBUTION OF THALLIUM IN TISSUES, BLOOD, URINE AND FECES

CHAPTER I

INTRODUCTION

Although thallium is relatively rare, it has become a widely used element. There are many industrial uses. Thallous chloride has been mixed with tungsten used for filaments in electric light bulbs since this mixture was found to prolong the life of tungsten lamps (1). Metallic thallium as a constituent of glass gives it a high refractive index required for optical purposes and imitation gems (2). A thallium-silver alloy has been found to be stainless (3), and an amalgam of thallium is used in thermometers for registering temperatures as low as -60 degrees centigrade (1).

Today, the principal use of thallium is as a constituent of insecticides and rodenticides. Thallium salts were used as rodent poisons in Germany as early as 1920, and a preparation containing approximately two per cent thallium was placed on the market under the trade name "Zelio Paste" or "Celio Paste." The United States Department of Agriculture, in 1925, approved the use of thallium for the control of rodents, particularly certain species of prairie dogs and ground squirrels that had refused to take strychnine baits. The preparation placed

on the market was a barley grain product, "Thalgrain," containing one per cent thallium. In the past few years a variety of insecticidal and rodenticidal preparations destined for household use have appeared on the market (4). Periodically, episodes of poisoning associated with these pesticides focus attention on the nature of this economic poison, especially when it is used around the home.

Thallium has been used without success in the treatment of syphilis (5) and night sweats of phthisis (6). The successful application of thallium, as the acetate salt, in past years was as an epilating agent in the treatment of ringworm in children or as a depilatory cream. Approximately fifty years ago Sabouraud, a French authority on diseases of the hair and scalp, prescribed an ointment of thallium acetate for the removal of superfluous hair (7,8). This prescription called for not more than one per cent of thallium acetate. Sabouraud urged that even in this dosage it should be applied only once a day, and that an amount of the ointment no larger than two kernels of wheat should be used. A few years later, in 1930, Kora M. Lublin marketed a depilatory under the name of "Koremlu Cream" (9) which was "guaranteed to devitalize superfluous hair roots on face or any part of the body." This preparation contained seven per cent thallium acetate. The indiscriminate use of this cream as the result of false advertising led to many cases of thallium intoxication (10). Buschke (11) and others (12, 13, 14, 15) recommended the oral administration of thallium salts for epilation of children prior to the treatment of tinea capitis. However, several cases of poisoning from the medicinal use of thallium have been reported (16, 17), and many accidents have resulted from miscalculation of the

dosage (18, 19). The medicinal and cosmetic application of thallium salts has been completely discarded because of its toxicity.

The areas of thallium poisoning may be summarized as follows:

Industrial. In industry, the personnel and particularly the industrial medical staff are aware of the toxic properties of thallium and of the proper precautions that are necessary to prevent poisoning. Special working clothes and gloves are worn, and masks to prevent inhalation of thallium containing dusts are often used. Periodic physical examinations are required. Should the worker show symptoms of thallium intoxication, he is transferred to another job within the plant. At a later date the worker might be returned to his original job. This awareness and precaution by industry has been successful. No deaths from industrial exposure to thallium have been reported in the literature (20, 21, 22, 23).

Therapeutic. Both fatal and non-fatal poisonings have been reported as a result of either the internal or external administration of thallium salts for the production of alopecia in the treatment of ringworm and favus, and in the management of the night sweats of phthisis. Realization by the medical profession of the toxicity of thallium has led to the discontinuance of thallium salts as therapeutic agents.

Accidental, homicidal or suicidal. Since thallium containing preparations have been and are available in the open market without proper regulation, the public has ready access to them. Thus, accidental poisoning occurs, and homicidal and suicidal "accidents" may easily be perpetrated. One case on record is that of a woman who spread Zelio paste on her husband's sandwiches. After a period of time the husband

became ill and displayed vague symptoms of a neurological nature. After hospitalization, he returned to work and his wife repeated her "special sandwich." Again her husband became very ill and was hospitalized. This time there was a loss of hair, and homicidal thallotoxicosis was suspected. When the wife was confronted with laboratory proof of the presence of thallium, she confessed to her part in the attempted murder.

Therefore, one sees that the industrial and therapeutic management of thallium does not present a particularly critical problem since industry and the medical profession are cognizant of the toxic nature of thallium and handle it with discretion or do not use it. The accidental, homicidal and suicidal use or misuse of thallium has been and remains a serious problem. This concern has a firm basis as documented by the incidents of thallium intoxication in children in Texas and Louisiana (24, 25, 26, 27) during the past two years. Other states, particularly in the southwestern and western United States, are showing an increase in thallium poisonings (28). In Europe, thallium is replacing arsenic as the "drug of choice" for homicide (28, 29).

This new choice is logical since thallium imparts no color to a solution, is tasteless and odorless, and difficult to detect. A further mark of its insidious nature as a poison is the delayed and undistinguished character of its symptoms. It is difficult to diagnose and treat thallium intoxication or prevent the disabling aftereffects. Without the diagnostic appearance of alopecia or the outright admission of one who has intimate knowledge that thallium was administered, a definitive diagnosis of thallium poisoning is nearly impossible. This is true since pains and disturbances are easily interpreted as stemming

from or mimicking other diseases. An example of this is given by Prick et al. (29) who recorded the case of a woman who attempted the murder of thirteen people and was successful seven times. The death certificate of each person carried a different diagnosis as to the cause of death. The legitimate use of thallium today, other than industrial, is in the control of rodents and insects which reject baits containing other substances such as arsenic, rotenone, and strychnine. The preparation of thallium containing compounds such as syrups and pastes in a one to five per cent concentration for use alone or applied to foodstuffs such as bread, cookies, cake, nuts and cereals, presents a more serious aspect to the problem of thallotoxicosis. Unfortunately, these items are palatable to children and household pets. It also places a potent instrument in the hands of those intent upon homicide or suicide. Whatever the cause or purpose of the poisoning, a method quantitative for the determination of thallium is desirable. Such a method for the quantitative determination of thallium in tissues and body fluids which is accurate, specific, sensitive and simple is presented.

CHAPTER II

HISTORY

In March, 1861, in the course of the spectrographic examination of deposits on the flues from an oven at Tilkerode in the Harz Mountains, Germany, in which sulphur containing ores had been roasted, Crookes (30) observed a previously unknown green line (535.0 m mu) which he attributed to a new element. Because the color of the line suggested that of young vegetation, he gave the element the name "thallium" from the Greek word thallus meaning a budding twig. In April of the same year Lamy (31) independently discovered the same element in the sludge in the lead chambers of a factory producing sulphuric acid at Loos, France. During the following year Crookes (32) and Lamy (31) investigated the chemical properties of thallium.

In the periodic classification of the elements, thallium is placed in group three which, except for boron and aluminum, contains some of the rarest elements. Group three is subdivided into two groups, A and B, and thallium belongs to the latter along with gallium, indium, boron and aluminum (33). The small size and high concentration of nuclear charge give boron strictly non-metallic characteristics. The other elements of the family are all metals, with aluminum being particularly highly electropositive in nature. Thus, between boron and aluminum there is a

discontinuity in properties which is without parallel in other groups. This has presented certain problems which have made it difficult to establish the correct place of thallium in the periodic table. The chemistries of aluminum, gallium, indium and thallium are closely related. Boron chemistry resembles silicon chemistry more closely than the chemistries of the other members of its own family. The monovalent salts of thallium are more stable than the trivalent thallium salts which resemble those of boron and aluminum. Boron and aluminum function only as trivalent elements. There is also a marked resemblance of thallium to metals of other groups such as silver, potassium, mercury and lead.

Lamy was the first to isolate thallium in a pure state and he was also the first to recognize the toxicity of thallium. While engaged in his research, he suffered from general lassitude and weakness of the lower limbs, and this led him to test the toxicity of the sulphate of the new element by feeding it to dogs, ducks, and hens. The amount given is not recorded, but all of the animals died after having given evidence of intestinal and respiratory embarrassment, peripheral paralysis and general weakness (31). Crookes had doubts as to the toxicity of thallium and is said to have taken several grains of a thallium compound without suffering ill effects (34). Both Paulet (35) and Grandeau (36), after further experimentation, expressed the opinion that it was more toxic than lead.

Death of toads, mice, rats, rabbits, dogs, ducks, geese and quail have been reported as the result of the oral administration of one of the soluble thallium compounds in amounts equivalent to 6 - 40 mg. of the metal per kilogram of body weight (37, 38, 39, 40, 41). The available

data indicate that results were not greatly different when the subcutaneous, oral or intravenous routes of administration were employed, but the early papers do not tabulate positive results (42). Buschke and Pieser (43) found that organic compounds of trivalent thallium such as thallium dimethyl bromide was only one-tenth as toxic as thallous acetate when administered to mice. Iljin et al. (38), however, state that certain trivalent organic thallium compounds are among the most toxic compounds of this metal.

Thyresson (44) and Swain and Bateman (40) have offered evidence that the action of thallium is cumulative, especially in chronic exposure. The latter investigators found that the effects of administering 200 mg. of a thallium compound to a dog in divided doses over a period of thirteen days was as marked as those resulting from the administration of a similar amount in four days. Severe intoxication occurred in rats as a result of the oral administration of 0.2 mg. of thallium acetate per rat daily for several weeks (45). The statement that a tolerance for small amounts of thallium can be developed has been attributed to Marme (46), but no other investigators have observed this feature of thallium toxicity.

The distinguishing feature of the toxic response to thallium that has aroused the greatest interest is its ability to cause alopecia. According to Cushny (47), Richet (48) was the first person to record the fact that chronic poisoning by thallium was accompanied by epilation and generalized muscular atrophy although Sabouraud (7) is usually credited with this observation. About this time, 1898, Combemale (6) advocated the use of thallium acetate for colitis and for lessening the night

sweats of phthisis (tuberculosis). He found that several days after the administration of the thallium salt there was a complete and rapid loss of hair. This was confirmed by Huchard, Jeanselme and Guinard (34) on patients. However, Buschke, Lowenstein and Joel (49) showed on rabbits and guinea pigs that the onset of alopecia is delayed for a week or more and never occurs in animals that die within a few days after the administration of the thallium. Buschke and his co-workers published over 40 papers on thallium intoxication and epilation. They pointed out that the epilating effect is most marked on those hairs whose follicles are innervated by the sympathetic nerves. They maintained that the toxic action was mediated in some manner by alterations in the function of one or another of the ductless glands which in turn acted upon the sympathetic nervous system. This view, however, has been questioned by Leigheb (50), Truffi (51) and Thyresson (52). The present consensus is that the sympathetic nervous system is not involved in epilation, but that thallium acts directly on the hair follicle (53). Recent work by Baumann (54) and Lund (55, 56) presents a more acceptable basis for the mode of action of thallium. Baumann states:

> Tissues highly sensitive to short wave length radiation are also sensitive to karyoclastic poisons. This applies to the hair follicles, the thymus, the testicles, the spleen, the lymphatic glands and perhaps to other organs not yet investigated. The degree of sensitivity of the organs and tissues to Roentgen rays is largely the same as their sensitivity to karyoclastic poisons.

Lund found that thallium follows potassium in distribution and excretion in the body. Since potassium is distributed predominantly intracellularly in the body, and since thallium, which is toxic to the cell, follows potassium in distribution, thallium can be considered as a

generalized protoplasmic poison.

The signs of severe intoxication of animals by thallium - restlessness, tremors, ataxic gait, convulsive movements of the legs followed by partial paralysis, anorexia, loss of weight, constipation or bloody diarrhea, and dyspnea - are indicative of widespread damage to the nervous system and digestive tract, and to a lesser extent, the cardiovascular system. Symptoms of nervous dysfunction are commonly encountered and usually predominate over the gastrointestinal disturbances. Dixon (57) states that neurological signs are always delayed, the immediate action being limited to a relaxation of smooth muscles of the bronchioles, intestines and uterus. He found that direct application of thallium salts to the ganglion in the neck of the cat permitted subliminal stimuli to become effective, and from this and other experiments, Dixon concluded that thallium acts on both divisions of the autonomic nervous system as strychnine does on the central nervous system. Unfortunately, further work has not been reported to substantiate this concept.

In reviewing the literature, one is impressed by the lack of a common or basic concept of the meaning of the terms acute, subacute and chronic toxicity, particularly as related to thallium. The confusion is compounded when it is considered that many variables are involved. A digression at this point is appropriate in order to establish a definition for the terms in question.

A check of the toxicology, medico-legal and pharmacology books available failed to disclose a positive explanation of these terms when they were used. An exception is a booklet by George (58) on pesticides in which he defines two of these terms as applied to his field:

> Acute toxicity refers to toxic effects usually severe or lethal, immediately resulting from a single exposure to one application of a pesticide.

and

> Chronic toxicity refers to toxic effects resulting from multiple exposure to a single application or exposure to each of several applications over a period of time. Hence, when toxicity is cumulative, it is considered chronic.

Most authors do not illustrate their view this clearly, but depend upon the acceptance of a definition recorded by a vague predecessor who is never identified. Others simply imply what their definition or concept is. For example, Prick et al. (29) in their discussion of thallium poisoning make this statement regarding ten cases of thallotoxicosis:

> To the first (type) belong a number of acutely developing cases of illness ending in death after a week to ten days. The second group passed first through an acute phase and then into a chronic, much more quietly developing syndrome, which sometimes lasted six months or longer and showed new symptoms during this period. Between the acute form ending in death and the chronic form of the thallium intoxication we can place as a gradual transition the subacute form, extending over no more than from six weeks to three or four months.

Gettler and Weiss (37) illustrate their concept as to time and symptomatology. Excerpts are presented here:

> In the acute fatal cases, after taking a large dose, the symptoms are gastrointestinal colic, vomiting, trembling, convulsions followed by motor paralysis, dyspnea, collapse, and death in about thirty hours.
>
> In the subacute poisonings, where the patient lives for several days to three or four weeks, the symptoms that have been observed more commonly are . . .
>
> In chronic poisoning the only characteristic finding is alopecia (the falling out of hair). Other symptoms that have been observed are . . .

In a discussion on the toxicity of Trancopal^{R}, Winthrop Laboratories presented this information (59):

ACUTE TOXICITY The twenty-four hour LD_{50} was computed to be 1680 $\pm$ 206 mg./kg. Toxic doses caused ataxia, sedation and narcosis, and death from respiratory arrest occurred within two to four hours after medication, with some deaths delayed up to the seventh postmedication day.

SUBACUTE TOXICITY Trancopal was tolerated by albino rats when given in an oral dose of either 314 or 501 mg./kg./day for five consecutive days, but was not well tolerated in daily doses of 795 and 1000 mg./kg. . . . Deaths due to severe depression occurred within two to four days at doses of 795 and 1000 mg./kg./day.

CHRONIC TOXICITY In a one year study of chronic toxicity on oral administration in monkeys, Trancopal was given in single daily doses of 10, 30, and 90 mg/kg. The only pharmacologic response to the drug was descending depression of the spinal cord which resulted in ataxia at the highest dosage level.

Fairhall (60) in the introduction of his book, Industrial Toxicology, says

> It will be apparent therefore that the term toxicity does not refer to a fixed quantity, such as, say, a constant of nature. On the contrary, it is a descriptive term and is more often clearly understood when applied in relation to other analogous substances.

If one turns to the generally accepted standards such as Dorland's Illustrated Medical Dictionary and Webster's Unabridged Dictionary, these definitions are found:

Acute - "attended with symptoms of some degree of severity, and developing rapidly or coming speedily to a crisis."

Subacute - "between acute and chronic, but with some acute features."

Chronic - "continuing for a long time; of a disease, of long duration or characterized by slowly progressing symptoms."

It should be evident from the preceding quotations that no single, simple definition is adequate to express the meaning of each term. Therefore, rather than become lost in words, the definition of the terms involved are presented in a tabular form in Table 1. From this table a better understanding of the terms acute, subacute and chronic may be ascertained.

TABLE 1

CLASSIFICATION OF TOXICITY

Class	Dosage or Exposure	Latent Period	Symptoms
Acute	Single	Short	Severe
Acute	Multiple at Short Intervals	Short	Severe
Acute	Single	Long	Severe
Acute	Multiple at Short Intervals	Long	Severe
Subacute	Single	Short	Mild
Subacute	Multiple at Short Intervals	Short	Mild
Subacute	Single	Long	Mild
Subacute	Multiple at Short Intervals	Long	Mild
Chronic	Multiple over a Long Interval	Long	Severe
Chronic	Multiple over a Long Interval	Long	Mild

The use of the terms acute, subacute and chronic in this paper will correspond to the foregoing table, and where sufficient evidence warrants a change from that found in the literature, the terminology will be changed to agree with this concept.

At necropsy, the predominant lesions are in the digestive tract (61, 62), nervous system (62, 63, 64, 65) and kidneys (65). Lesions are also found in other organs and tissues.

Histological examination by Prick et al. (29) in several cases of acute poisonings where death had occurred, found degenerative changes in the peripheral nervous system whereas the central nervous system was but slightly affected. Many peripheral nerves showed an irregular appearance and vacuolization of the axis cylinders. Other neurons were disrupted and swollen, and myelin degeneration and swelling of Schwann's cells were reported.

In subacute poisonings there may be disorders in addition to those previously mentioned, namely; congestion of the cerebral meningeal blood vessels, hyperemia, parenchymatous degeneration, granular and fatty degeneration of internal organs, and edema and congestion of the lungs.

In chronic thallium poisoning the central nervous system shows marked changes. These changes are characterized by edema, a decrease in the number of ganglion cells, a paucity of cells in the nuclear areas of the brain with nuclear malformation, tigrolysis, vacuolar degeneration and chromatolysis.

In Table 2 most of the histological changes found at autopsy on human beings and animals after poisoning by thallium are summarized.

The acute, profound intoxication which follows ingestion of

TABLE 2

HISTOLOGICAL CHANGES AFTER
THALLIUM POISONING

Organ	Parenchymatous Degeneration	Fatty Infiltration	Hemorrhage	Congestion
Heart	61, 62	29, 37		
Liver	50, 61, 63	29, 37		
Kidney	41, 50, 61, 65	29, 37	50, 63	
Spleen				
Pancreas	41, 50		50	
Testes				
Ovaries				50
Thyroid	50, 95, 96		50	50
Lungs				50, 63
Muscle			48, 50	
Stomach			41, 50	50
Small Intestine				50
Large Intestine				50
Adrenal			63	63
Pituitary				50
Eye			49	
Parathyroid	63			
Skin	51, 57			
Sweat Glands				
Brain				

Numbers refer to specific bibliographic references giving information on histological changes.

TABLE 2-Continued

Edema	Inflammation	Karyolysis	Vacuolation	Necrosis	Atrophy
29					
65				29, 41, 50	
	29	54			
	41, 50	41, 50			
		54		49, 54	
50	50				
					48
	41, 50				
	29				
	29				
		63	63		
	49, 67			49	67, 97
		50, 54		50	
		54		50	
29		29	29		

lethal amounts of thallium salts has been well documented by Ginsberg and Nixon (66) in their report on eleven cases of thallotoxicosis resulting from the ingestion of tortillas made from "Thalgrain." Vomiting, paresthesia and severe cramps with diarrhea developed within twenty-four hours after eating the contaminated food. Stomatitis was marked, salivation was increased, the breath was foul and there were blebs on the lips. In some cases there was a purple line at the gingivodental margin. Within five days all patients showed signs of cerebral involvement. A chemical encephalitis with evidence of injury to the cranial nerves, choreiform movements and muscular twitching developed. Convulsions and delirium were noted in the more severe cases. A terminal rise in temperature was noted. Death was attributed to respiratory failure.

Depending on the degree of intoxication, paralysis with diminution in reflexes may supervene. The most commonly reported sign of this type is foot drop. Paresthesia and hyperesthesia occur in the arms and legs, but these symptoms are usually more marked in the lower extremities. There may also be pains in the thorax and joints. Another serious consequence is optic neuritis (67, 68). Malaise, insomnia and agitation may exist. Constipation or obstipation usually is present, but diarrhea can occur. Later the skin may become thick and scaly, especially on the lower limbs. These symptoms may run a course of several days to several weeks, and epilation usually begins during the third week thus revealing a definite diagnostic clue. Laboratory findings in such cases often will reveal a leukocytosis, erythropenia, albuminuria (20) and the presence of thallium in the urine. The methods for the detection and quantitation of thallium in the urine, feces and tissues are varied. A brief

description of several methods for the quantitative determination of thallium are summarized:

Gravimetric Methods

Weighing as Thallous Iodide or Thallous Bromide (69)

The thallium in solution is precipitated as thallous bromide or iodide by the gradual addition of a solution of hydrogen bromide or hydrogen iodide respectively. The precipitate is collected by means of a Pregl filter tube, and washed first with a solution of hydrogen bromide or hydrogen iodide, and then with acetone. The precipitate is dried at 80 to 100 degrees centigrade for one hour while passing filtered air through the tube, and is then weighed.

Weighing as Thallic Oxide (70)

The thallium is precipitated as thallic hydroxide by potassium hydroxide plus potassium ferricyanide or by ammonium hydroxide plus bromine. The precipitate is collected by filtration in a Gooch crucible, washed, dried at 200 degrees centigrade and weighed as thallic oxide.

Weighing as Thallous Chromate (71, 72)

The solution containing the thallous ion is made ammoniacal, heated to 70-80 degrees centigrade, and a solution of potassium dichromate is added while stirring. After standing twelve hours, the precipitate is collected in a Gooch crucible, washed with a one per cent chromate solution, and with alcohol, and is then dried and weighed.

Colorimetric Methods

Dithizone (73)

The procedure is similar to that for lead. The red, chloroform solution of the thallium - dithizone complex is collected, washed, made to definite volume with chloroform and the color read against a similarly prepared standard or by means of a photoelectric colorimeter.

Liberation of Free Iodine (74, 75)

The thallium is oxidized to the thallic state with bromine. Excess oxidizing agent is removed. A small excess of potassium iodide is added. The thallic ions liberate an equivalent amount of free iodine. The latter is extracted with carbon disulfide, made to a definite volume, and the color read in a colorimeter against a standard iodine solution in carbon disulfide.

Reaction with Phosphomolybdic Acid (76)

The blue color obtained by adding phosphomolybdic acid and a strong solution of hydrogen bromide to a solution containing thallous ions is read in a colorimeter against a standard thallous solution similarly prepared.

Volumetric Methods

Titration with Permanganate (77)

The solution containing thallous ions is made alkaline with potassium hydroxide. A measured quantity of standard potassium ferricyanide is added. The thallous ions present reduce an equivalent amount of potassium ferricyanide to potassium ferrocyanide, which is then titrated with a standard potassium permanganate solution.

Titration with Ceric Sulphate (78)

The procedure is similar to that of the permanganate method except that ceric sulphate is used in place of potassium permanganate.

Titration with Bromate Solution (79)

The thallous ions in hydrochloric acid solution are titrated with a standard bromate solution using methyl orange as the indicator.

Iodometric Method (80)

The thallium is oxidized to the thallic state with bromine. Excess oxidizing agent is removed. Potassium iodide is then added. The thallic ions liberate an equivalent amount of free iodide which is then titrated with standard sodium thiosulphate solution.

Most of these methods are adapted to the quantitative determination of fairly large amounts of thallium, but are, in many instances, not sufficiently sensitive to determine the micro quantities found in tissues. In addition, the reactions involved are not specific for thallium. A method that is specific and sufficiently sensitive for determination of very small amounts is necessary.

CHAPTER III

METHODS AND PROCEDURES

The method presented here for the determination of thallium is founded partly upon familiar principles and partly upon other principles published earlier but not utilized. Canneri and Perina (81, 82) state that upon the addition of potassium iodide to an acid solution containing thallium (I)[1] and bismuth, thallium-bismuth iodide, $(TlI)_2.BiI_3$, separates quantitatively as wine-red microcrystals. Ice and Shoemaker (83) developed a procedure for the determination of thallium in biological tissues and fluids based upon this principle. The thallium was precipitated by the addition of a solution containing bismuth nitrate and potassium iodide. The precipitate was filtered, washed and dissolved by a solution containing sulphuric acid and sodium nitrite. The iodine was removed by boiling and the solution acidified with hydrochloric acid. A small amount of chloroform was added and the aqueous solution titrated with 0.01N potassium iodate. This method showed an accuracy of $\pm$ 2 per cent in the range of one to ten milligrams of thallium.

Reith and Gerritsma (84) described a method for the determination of thallium in tissues and fluids. It was based upon partial destructive oxidation with potassium chlorate and hydrochloric acid, extraction with

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[1] Thallium (I) indicates the thallous or monovalent state of thallium. Thallium (III) indicates the thallic or trivalent state of thallium.

ether as thallic chloride, removal from the ether layer as thallous chloride with water containing sulphur dioxide, and destruction of minute quantities of accompanying organic substances by a wet ashing procedure. The thallium was precipitated as thallous iodide and isolated by centrifuging. The precipitate can be determined gravimetrically or volumetrically by a procedure which incorporates an iodometric titration, and is useful for the quantitative determination of from 0.01 mg. to 5 mg. of thallium.

Another method for the quantitative determination of thallium is presented here. A weighed sample of biological material (2-15 gm.) is placed in a 50 ml. Kjehldahl flask, and sulphuric and nitric acids added. Five ml. of concentrated sulphuric acid is sufficient for the entire ashing procedure, and ten ml. of concentrated nitric acid is suitable for starting the digestion. The samples are permitted to set at room temperature for a few hours or until the tissues are in solution. Accelerated digestion by the immediate application of heat will cause foaming and frothing, and possible loss of thallium by overflow. The use of a slightly larger flask might prevent the overflow, but a quantitative transfer becomes difficult. When the sample is fluid, it is heated gently until there is no further frothing. More heat is applied, and nitric acid is added dropwise when the solution discolors from charring. The addition of nitric acid and heating is continued until no further charring appears. The solution is heated until the fumes of sulphur trioxide appear. If the solution does not discolor at this time, it is set aside to cool. After cooling, ten ml. of distilled water are added to the solution which is again heated until sulphur trioxide fumes appear. When the solution

has cooled, it is transferred quantitatively to a 25 ml. or 50 ml. volumetric flask and brought to volume.

A two ml. aliquot is taken for analysis. The thallium is brought down as a complex with an excess of precipitating solution (10 ml. of one per cent bismuth nitrate, two grams of potassium iodide, and five grams of sodium bisulfite, in a total volume of 100 ml.) in a small tube suitable for centrifugation. The precipitate formed is thallium-bismuth iodide, $(TlI)_2.BiI_3$, which has a characteristic wine-red (red-brown) color. The sample is centrifuged at 568 R. C. F. (Relative Centrifugal Force) (85) for fifteen minutes. The supernatant liquid is checked for completeness of precipitation and discarded. If the thallium content of any two ml. aliquot is more than 3 mg., a film of the precipitate is formed on the surface of the liquid which does not sediment upon centrifuging. This would cause a loss if it were poured off with the supernatant fluid. A drop of amyl alcohol will aid in dispersing the precipitate, but it is best to keep the total amount of thallium in the original aliquot less than 250 mcg. For this amount, one ml. of precipitating solution is considered an excess. The sides of the tube and the precipitate are washed with two ml. of water, and centrifuged at 568 R. C. F. for fifteen minutes. The water is poured off, and the precipitate is washed successively with two ml. portions of 50 per cent ethanol and 90 per cent ethanol at twenty degrees centigrade, and centrifuged each time at 568 R. C. F. for fifteen minutes. The sample is then dried in the centrifuge tube in an oven at 100 degrees centigrade.

Two-tenths ml. of glacial acetic acid, and one to two drops of bromine (from a fine pipette) are added. The mixture is warmed in a wate

bath until the precipitate is in solution. This requires approximately ten minutes. The solution is transferred to a 25 ml. Erlenmeyer flask with several washings of distilled water totaling not more than 2-3 ml., and warmed gently to a light yellow color which indicates that the major portion of the excess bromine has been expelled. The oxidation is rapid in the presence of bromine in glacial acetic acid. The reaction (33, 82, 84) is:

$$(TlI)_2.BiI_3 + 17\ Br_2 + 15\ H_2O \longrightarrow$$
$$2\ Tl^{+++} + Bi^{+++} + 5\ IO_3^- + 30\ H^+ + 34\ Br^-$$

Sodium formate (2M) is added until the solution is colorless, and 0.2 ml. is added in excess. The remaining bromine is removed by the addition of the sodium formate which forms an acetic acid - formate buffer. The solution is carefully mixed, making certain that the walls of the flask are moistened. The solution is allowed to set for five minutes.

Two ml. of sodium chloride (30 per cent) are added for two reasons: (a) the more stable $TlCl_4^-$ is formed (86), and (b) the color change during the titration of large amounts of thallium is more distinct and abrupt. Added successively are: one drop of a ten per cent potassium iodide solution, 0.2 ml. 4N sulphuric acid and five drops of a 0.2 per cent starch solution. The iodine liberated in the reaction below is titrated with 0.01N sodium thiosulphate solution, one ml. of which is equivalent to 120.2 mcg. of Tl^+. The reaction is:

$$2\ Tl^{+++} + 5\ IO_3^- + 29\ I^- + 30\ H^+ \longrightarrow$$
$$2\ Tl^+ + 17\ I_2 + 15\ H_2O$$

Titration of the samples with sodium thiosulphate was accomplished with an Aloe Model SB-1 Syringe Microburet fitted with a syringe calibrated

to deliver one ml. per inch of travel of the plunger. In place of the glass titrating tip, a Luer-Lok extension bent to a right angle was used as an adapter, and a 27-gauge needle with the needle tip finished square was used as the titrating tip. One drop had a volume of 0.007 ml. The tip can be placed beneath the surface of the liquid, and smaller amounts of solution may be delivered for titration without fear of contamination of the titrating solution.

In the presence of more than 250 mcg. of thallium per two ml. of solution, the color change upon titration is from blue through green to light yellow. This takes place slowly, probably, because the precipitate retains traces of iodine by adsorption (84).

A statement was made above that the reagent used to precipitate the thallium as a complex with bismuth is specific for thallium. As a test of the specificity, solutions of antimony, arsenic, copper, iron, lead, mercury, and tin were made in a concentration of one milligram per milliliter. Sufficient sulphuric acid was added to produce an acid concentration equivalent to the digestion mixture. The lead was precipitated as the sulphate. The filtrate did not contain enough lead to interfere with the test. Enough copper was present in the test solution to turn it blue. A white-gray precipitate was formed momentarily, but was dissolved in the excess potassium iodide in the reagent. Mercury formed a salmon-pink precipitate which dissolved in thirty to sixty seconds. Antimony, arsenic, iron, and tin did not form precipitates or interfere with the test.

If contamination by large amounts of heavy metals is known or suspected, the procedure described by Reith and Gerritsma (84) for the

separation of heavy metals from thallium can be applied, or separation by dithizone extraction (87) is possible.

The validity of the method outlined will be seen from the following test analyses. Two series of samples ranging from 10 to 250 mcg. of thallium (I) were analyzed using direct bromine oxidation, and precipitation-bromine oxidation as described. The thallium content of six samples was determined for each of the seven points by each of the two methods, and the means of each of the seven points by the two methods are recorded in Table 3. The means of the results of the precipitation-oxidation method described herein are plotted in Figure 1.

An additional test of this method was made on fifteen-gram samples of ground beef to which known amounts of thallium (I) had been added. Duplicate samples were run at each point selected and triplicate analyses were performed on each duplicate sample, thus giving six analyses per point. The figures in Table 4 represent the means of these points and are plotted in Figure 1.

A statistical evaluation of the procedure using the information in Table 4 shows that the variables X (Thallium) and Y (Thiosulphate) are linearly related (See Figure 1, where the symbol 0 represents the mean of six observations at each given value of X). This was confirmed by analysis of the sums of the squares due to regression (i.e. removed by), and it was found that 99.79% were due to linear regression. The coefficient of correlation (r) between X and Y is 0.998, indicating a highly significant positive relationship (association).

Linear regression based on the model of $Y = \alpha + \beta X + \epsilon$ (87) yielded a = 0.003754 and b = 0.0085614, where a = the unbiased estimate

of α and b = the unbiased estimate of β. For completeness, the following data are included:

ΣXY =	7106.42	ΣY^2 =	61.04
ΣX =	4680.00	Σxy =	2624.205715
ΣY =	40.225	Σx^2 =	306,514.2858
ΣX^2 =	828,000.00	Σy^2 =	22.514805

$$b = \frac{\Sigma xy}{\Sigma x^2} \qquad a = \bar{Y} - \beta\bar{X}$$

From this, given an X value, a value Y ($\hat{Y}$) may be predicted from the regression equation $Y = a + bX$. This has a variance of:

$$s^2_{\hat{Y}} = s^2_{y.x} \left[\frac{1}{n} + \frac{(x - \bar{x})^2}{x^2} \right]$$

where $s^2_{y.x} = \frac{\Sigma d^2_{y.x}}{n - 2}$ and $\Sigma d^2_{y.x} = y^2 - \frac{(\Sigma xy)^2}{\Sigma x^2}$

Confidence intervals were set on Y for various values of X within the range of this experiment using the following:

$$\hat{Y} - t_{.05}\, s_{\hat{Y}} \leq \mu \leq \hat{Y} + t_{.05}\, s_{\hat{Y}}$$

The confidence belts arrived at from the above are drawn about the regression line as interrupted lines in Figure 1. In general, the predicted value of Y ($\hat{Y}$) from a given X value has a remarkably small range of error and this method is thought to be quite satisfactory for predictive purposes. Examples of this for various ranges of X are as

follows:

when X (Tl in mcg.) equals	Y (ml. of 0.01N thiosulphate) equals
10	0.089 ± 0.016
50	0.432 ± 0.013
150	1.288 ± 0.011
250	2.144 ± 0.020

TABLE 3

COMPARISON OF METHODS

	Precipitation as TlI and Oxidized with Bromine		Precipitation as Complex and Oxidized with Bromine	
Tl Added (mcg.)	Tl Recovered (mcg.)	Per Cent Recovery	Tl Recovered (mcg.)	Per Cent Recovery
10.0	10.2	102.0	9.9	99.0
20.0	20.2	101.0	19.9	99.5
50.0	48.8	97.6	49.3	98.6
100.0	98.9	98.9	99.0	99.0
150.0	152.0	101.0	150.1	100.1
200.0	199.8	99.9	198.6	99.3
250.0	247.3	98.9	248.1	99.2

TABLE 4

RECOVERY OF THALLIUM(I) ADDED TO GROUND BEEF AND DETERMINED BY PRECIPITATION AS $(TlI)_2.BiI_3$

Tl Added (mcg.) (X)	Tl Recovered (mcg.)	Per Cent Recovery	Na Thiosulphate (ml. 0.01N) (Y)
10.0	10.3	103.0	0.094
20.0	20.1	100.5	0.194
50.0	51.8	103.6	0.454
100.0	96.0	96.0	0.823
150.0	143.8	96.0	1.246
200.0	196.3	98.2	1.701
250.0	252.6	101.0	2.189

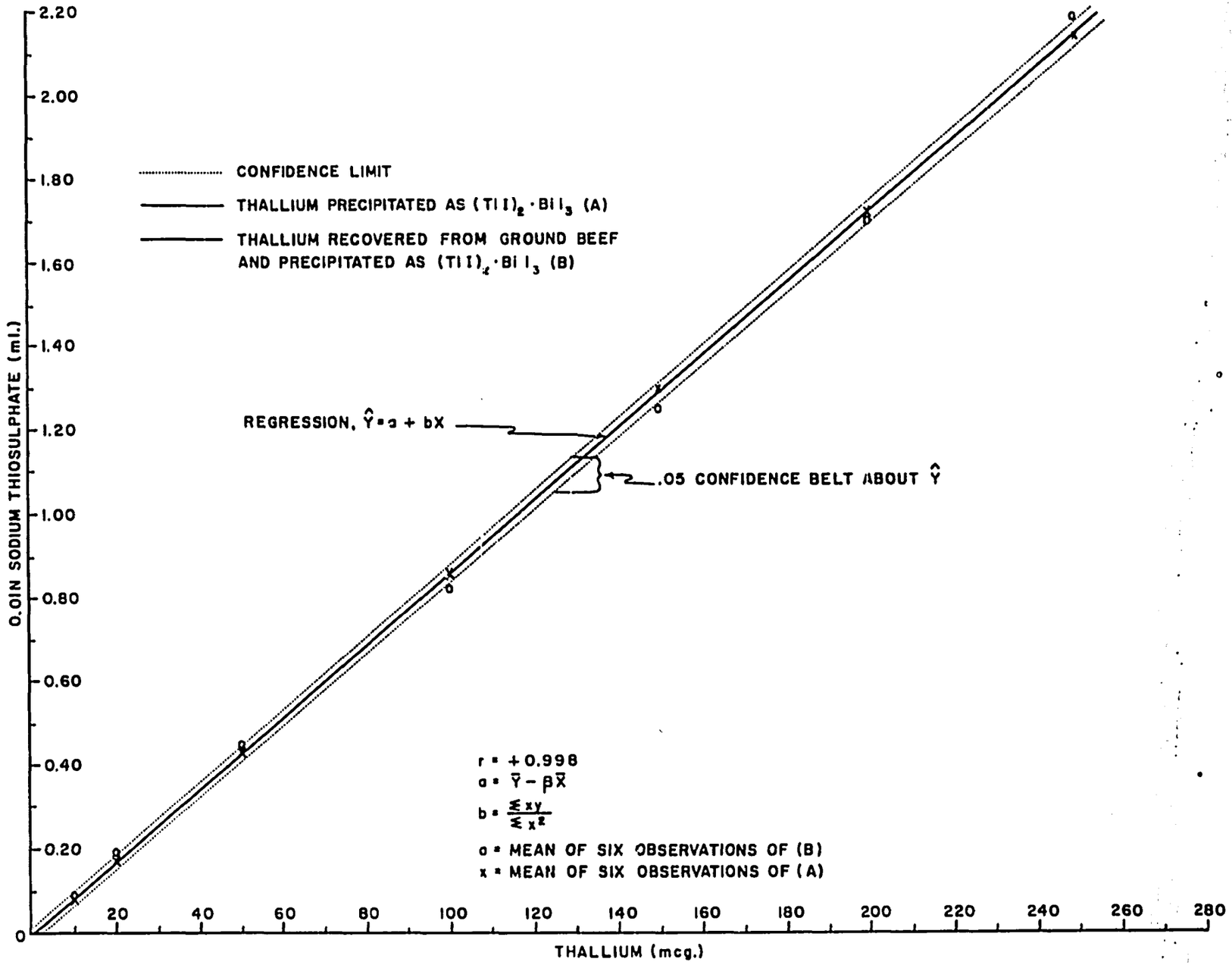

2.20
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0
0.01N SODIUM THIOSULPHATE (ml.)
CONFIDENCE LIMIT
THALLIUM PRECIPITATED AS $(TlI)_2 \cdot BiI_3$ (A)
THALLIUM RECOVERED FROM GROUND BEEF AND PRECIPITATED AS $(TlI)_2 \cdot BiI_3$ (B)
REGRESSION, $\hat{Y} = a + bX$
.05 CONFIDENCE BELT ABOUT $\hat{Y}$
$r = +0.998$
$a = \bar{Y} - \beta\bar{X}$
$b = \frac{\Sigma xy}{\Sigma x^2}$
o = MEAN OF SIX OBSERVATIONS OF (B)
x = MEAN OF SIX OBSERVATIONS OF (A)
20
40
60
80
100
120
140
160
180
200
220
240
260
280
THALLIUM (mcg.)

FIGURE I

CHAPTER IV

RESULTS AND DISCUSSION

Four female mongrel dogs were used for determining the distribution of thallium in tissues, body fluids and feces in acutely and chronically intoxicated animals. Two animals were used for the acute study and two were used for the chronic study.

Acute Toxicity

The two dogs were anesthetized with pentobarbital sodium (30 mg. per kg. - I.V.). The right carotid artery was cannulated and the blood pressure recorded using a mercury manometer connected to a cannula by means of a heavy wall tubing. The system was filled with five per cent sodium citrate to inhibit clotting. The trachea was cannulated to maintain an open airway. The femoral vein was cannulated with polyethylene tubing which was attached to a Luer-Lok-Coupler which adaps to any syringe. Constant infusion of the thallium sulphate solution was made through this tubing by the use of a constant rate injecting machine set to deliver the proper amount of thallium at a predetermined rate.

Animal number one weighing 6.81 kg. was infused at the rate of 1.75 mg. Tl^{+}/kg./min. (11.92 mg. Tl^{+}/min.) until the animal died. This animal lived two hours and twenty minutes. The total amount of thallium (I) administered to this animal was 1.668 grams, or 245 mg./kg. Urine

samples were collected directly from the bladder by quantitative washing at thirty minute intervals, and analyzed for thallium. These results are shown in Table 5.

General findings at autopsy showed edema and acute passive congestion of the lungs. None of the other organs appeared to be abnormal. Tissues were collected after autopsy and analyzed for thallium. The amount of thallium found in the tissues and expressed as mg. Tl^{+}/100 gm. of tissue is shown in Table 9 and Figure 2.

Animal number four weighing 7.73 kg. was infused at the rate of 1.0 mg. Tl^{+}/kg./min. (7.73 mg. Tl^{+} min.) until the animal died. This animal lived four hours and thirteen minutes. The total amount of thallium (I) administered to this animal was 1.956 grams or calculated on a weight basis, 253 mg./kg. Urine samples were collected directly from the bladder at thirty minute intervals and analyzed for thallium. These results are shown in Table 6.

General findings at autopsy again showed edema and acute passive congestion of the lungs. No other changes were apparent upon gross examination. Tissue samples were collected at autopsy and analyzed for thallium. The amount of thallium found in the tissues and expressed as mg. Tl^{+}/100 gm. of tissue is shown in Table 9 and Figure 2.

Three significant facts are observed. Urinary excretion of thallium begins within thirty minutes, and in animal number one thallium is present in the urine in twenty minutes. Renal shutdown occurs after the first hour in animal number one, and after the third hour in animal number four. It has been well established that the primary route of elimination of thallium is via the kidneys, but such a rapid appearance in the

URINARY EXCRETION OF THALLIUM IN ACUTE TOXICITY

TABLE 5

ANIMAL NO. 1

Sample Number	Time Withdrawn	Urine Volume	Thallium mg./100ml.
1	11:30 am	80 ml.	0.00
2	12:00 pm	65 ml.	0.00
3	12:30 pm	50 ml.	0.00
Thallium Sulphate Started at 12:40 pm (1.75 mg. Tl /Kg./min.)			
4	1:00 pm	50 ml.	25.4
5	1:30 pm	10 ml.	11.3
6	2:00 pm	0 ml.	0.00
7	2:30 pm	0 ml.	0.00
8	3:00 pm	Death	Death

TABLE 6

ANIMAL NO. 4

Sample Number	Time Withdrawn	Urine Volume	Thallium mg./100ml.
1	11:15 am	75 ml.	0.00
Thallium Sulphate Started at 11:30 am (1.0 mg. Tl /Kg./min.)			
2	12:00 pm	29 ml.	1.18
3	12:30 pm	16 ml.	37.4
4	1:00 pm	18 ml.	58.8
5	1:30 pm	23 ml.	39.5
6	2:00 pm	34 ml.	19.1
7	2:30 pm	48 ml.	10.4
8	3:00 pm	14 ml.	9.5
9	3:30 pm	0 ml.	0.00
10	3:30 pm	Death	Death

urine is not recorded. However, when acute toxicity is produced by continuous intravenous infusion, it can be expected to differ from oral ingestion of large quantities of thallium salts. Another striking fact is the similarity in the amount of thallium that produced death in these animals. Animal number one died after receiving 245 mg./kg. of thallium. Animal number four died after receiving 253 mg./kg. of thallium. These are of even greater interest when one considers the fact that the concentration of the thallium solutions was different and the animals were of different weights.

Chronic Toxicity

Animals number two and three were placed in metabolism cages so that the urine and feces could be collected daily and analyzed for thallium. At the beginning of the experiment animal number two weighed 8.64 kg., and animal number three weighed 6.14 kg. Thallium sulphate was triturated with lactose, and this mixture was placed in gelatin capsules. The thallium contained in each capsule was based on a dosage of 5 mg./kg./day of thallium (I). Animal number two received 43.2 mg. thallium (I) per day orally and animal number three received 30.7 mg. thallium (I) per day orally until death occurred.

Animal number two was active, alert, friendly and cooperative at the beginning of the experiment. The animal ate heartily. On the second day there was evidence of diarrhea. Activity and intelligence appeared normal. On the third day, the animal was definitely ill, and constipated. It was reluctant to walk or stand, but would move when it was necessary by using the front legs. The rear legs were not used unless it was

absolutely necessary. The eyes were dull. A small quantity of food was eaten. On the fourth and fifth days, there was no perceptible change. On the sixth day, the dog preferred to lie down at all times and would not stand or respond to petting as usual. A diet of 100 per cent meat was substituted for the meat and meal mixture which had been the standard diet. The seventh day did not reveal any major changes nor any interest in the more pleasing diet. On the morning of the eighth day, the animal died.

At death the animal had received a total of 0.346 grams (40 mg./kg.) of thallium (I). The animal weighed 6.82 kg. - a loss of 1.82 kg. Gross examination at autopsy disclosed focal hemorrhages in the lungs, engorgement of the cerebral blood vessels, and showed the generalized effects of malnutrition caused by anorexia, and dehydration. Table 7 shows the analysis of urine and feces for thallium; Table 9 and Figure 2 show the distribution of thallium in the tissues.

Animal number three was also an active, friendly and cooperative dog. On the first and second days, this animal retained its normal character, activity and appetite. On the third day, the animal seemed to have lost weight, and was ill. It definitely preferred to remain in a prone position. On the fourth day, the animal was extremely ill, constipated, anorexic and ataxic. Its ribs were easily seen and felt, and the legs were also thin. On the fifth and sixth days increasing severity of symptoms was noted. On the seventh day, the animal was unable to coordinate its movements to walk. Before the last capsule could be given, the animal gasped and stiffened, and then gasped a few more times and died. This animal was cold to the touch ten minutes prior to death.

At death, this animal had received a total of 0.215 grams (35 mg./kg.) of thallium (I). It weighed 4.55 kg. - a loss of 1.59 kg. Gross examination at autopsy revealed approximately the same findings as seen in animal number two - focal hemorrhages in the lungs, engorgement of the cerebral blood vessels and the effects of starvation due to anorexia, and dehydration. The analysis of urine and feces is shown in Table 8, and the distribution of thallium in the tissues is shown in Table 9 and Figure 2.

Again, it is of interest to note that the results of urinary and fecal analysis are similar in the two animals. Glycosuria in both animals started on the third day, albuminuria occurred on the fourth and third days, respectively. Except for the initial episode of thin, watery diarrhea on the first day in animal number two, both animals became constipated. In both animals urinary excretion increased and then diminished to a state of anuria. Thallium excretion did not parallel urine volume.

As in the acute study where the lethal dose of thallium per kilogram was surprisingly close, the same situation is observed in the animals in the chronic study. Animal number two died from a total of 40 mg. of thallium (I) per kilogram, and animal number three died from a total of 35 mg. of thallium (I) per kilogram.

As indicated by the data recorded in Table 9, thallium was found to be distributed in nearly all of the organs and tissues contrary to the reports of many of the early workers such as Buschke. The pattern of distribution of thallium observed here agrees closely with that found by Gettler and Weiss (88), Fridli (89) and Thyresson (44). More recent work by Durbin et al. (90) and Heyndrickx (91) who used radio active thallium further supports the work presented here.

URINARY AND FECAL EXCRETION OF THALLIUM IN CHRONIC TOXICITY

TABLE 7

ANIMAL NO. 2

Day	Urine		Feces		Glucosuria	Albuminuria
	Volume ml.	Thallium mg./100ml.	Weight Gm.	Thallium mg./100ml.		
1	40	0.00	0*	0.00	Negative	Negative
2	60	0.00	0	0.00	Negative	Negative
3	115	0.53	16.7	0.00	1	Negative
4	260	0.87	25.1	0.00	Negative	Negative
5	73	5.40	0	0.00	2	Positive
6	87	8.60	0	0.00	2	Positive
7	0	0.00	0	0.00	...	...
8	0	0.00	0	0.00	...	...

* Diarrhea present, and feces were in urine.

TABLE 8

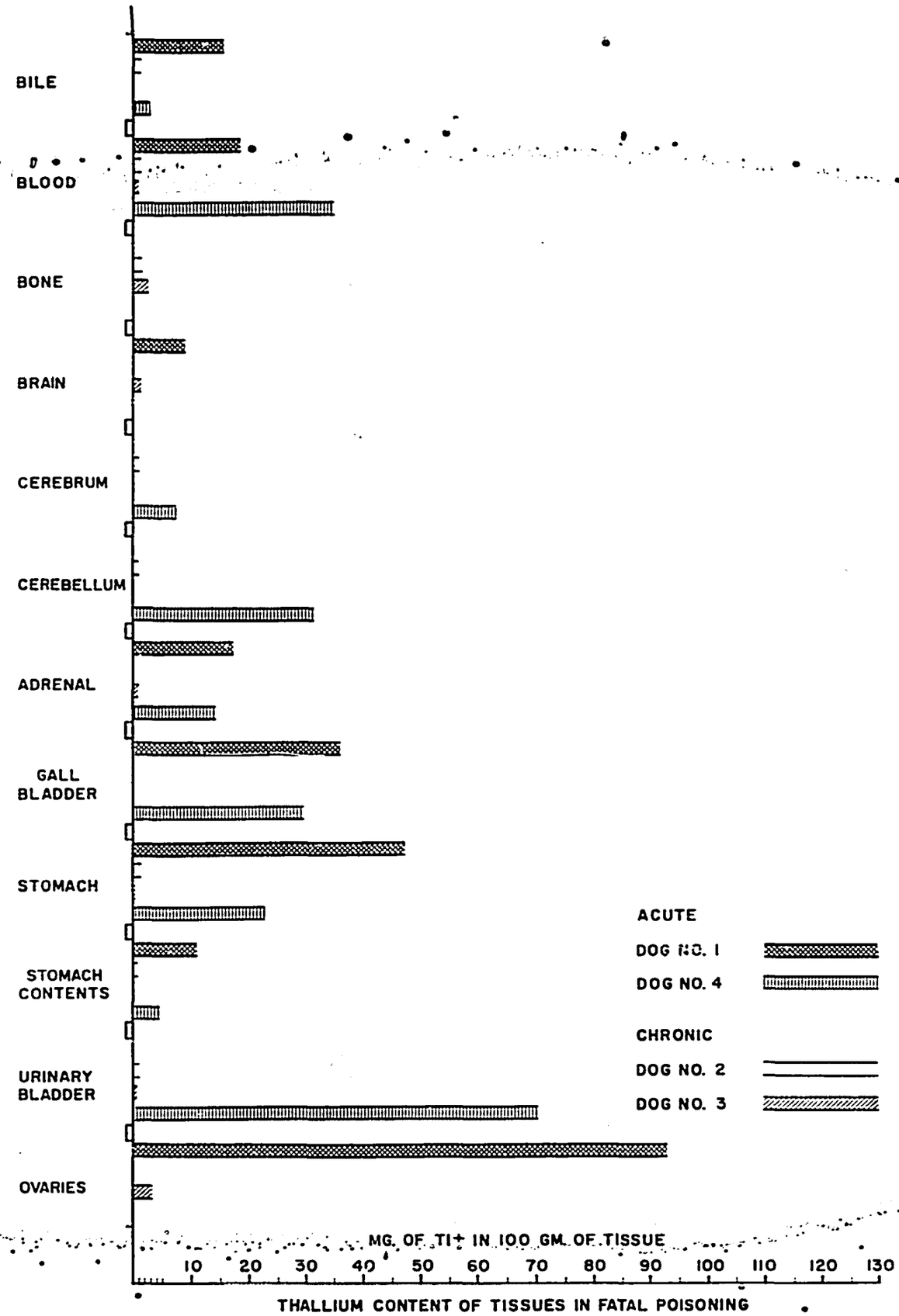
ANIMAL NO. 3

Day	Urine		Feces		Glucosuria	Albuminuria
	Volume ml.	Thallium mg./100ml.	Weight Gm.	Thallium mg./100ml.		
1	100	0.00	47	0.00	Negative	Negative
2	173	0.00	68	0.00	Negative	Negative
3	238	1.35	55	0.00	2	Negative
4	80	7.73	0	0.00	1	Positive
5	105	5.08	0	0.00	2	Positive
6	75	6.69	0	0.00	Negative	Positive
7	0	0.00	0	0.00	...	...

TABLE 9

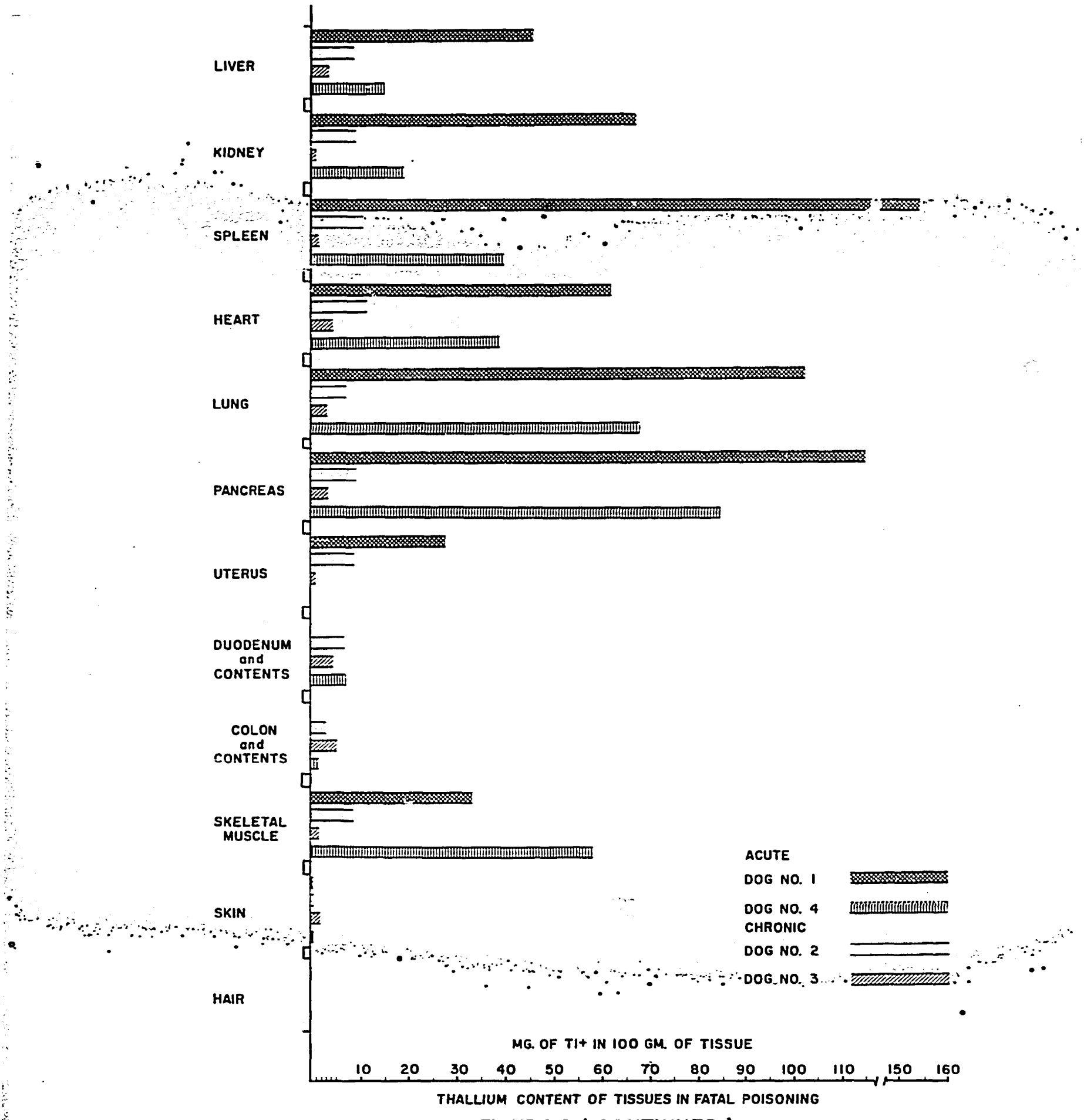
THALLIUM CONTENT OF TISSUES IN FATAL POISONING
(MG. OF Tl IN 100 GM. OF TISSUE)

Organ or Tissue	Acute		Chronic	
	Animal Number 1	Animal Number 4	Animal Number 2	Animal Number 3
Bile	15.5	2.94	1.10	Trace
Blood	18.5	34.7	1.07	0.58
Bone	0.0	0.0	1.75	2.71
Brain	8.84	...	...	1.61
Cerebrum	...	7.28	1.09	...
Cerebellum	...	31.5	1.05	...
Adrenal	17.3	14.4	Trace	0.56
Gall Bladder	35.7	29.5	Neg.	Trace
Stomach	47.0	22.6	1.49	0.15
Stomach Contents .	10.4	4.67	0.82	Trace
Ovaries	92.4	Castrated	Neg.	3.31
Urinary Bladder ..	...	70.1	1.04	0.56
Liver	44.7	14.4	8.37	2.44
Kidney	66.6	18.4	8.95	1.05
Spleen	154.0	39.6	10.2	1.60
Heart	61.3	38.4	10.7	4.30
Lung	102.0	67.2	7.01	3.20
Pancreas	115.0	83.9	9.28	3.40
Uterus	27.5	Castrated	8.33	1.04
Duodenum and Contents	...	6.85	6.36	4.54
Colon and Contents	...	1.33	2.74	5.07
Skeletal Muscle ..	33.1	58.0	8.50	1.35
Skin	0.57	0.45	0.50	1.80
Hair	0.0	0.0	0.0	0.0
Total dose of Tl expressed in Gm. given to each dog	1.668	1.956	.346	.215
Lethal dose of Tl (mg./Kg.)	245	253	40	35



THALLIUM CONTENT OF TISSUES IN FATAL POISONING

FIGURE 2



THALLIUM CONTENT OF TISSUES IN FATAL POISONING

FIGURE 2 (CONTINUED)

Thyresson states that in acute and chronic poisoning high or low concentrations of thallium may be found in all organs, and that thallium is excreted slowly after acute poisoning and accumulates in chronic poisoning. This statement is substantiated by the work shown here. The high concentration of thallium found in some organs in animals number one and four (acute poisoning) can be explained by the continual infusion of thallium, and the difference between animals is explained by the concentration of the thallium solutions used for infusing each animal. Other factors not readily apparent, such as the condition of the organ, might be a determining factor in the distribution of the thallium. The organs in these two animals which showed an increased uptake of thallium are, for the most part, highly vascular. There was a more even distribution of thallium in the chronically poisoned animals. This is true, in all probability, since there was more time for thallium to attain an equilibrium.

The wide-spread distribution of thallium in both the acute and chronic studies tend to corroborate Lund's belief (55) that thallium is similar to potassium in its distribution in the body. From the amount of thallium that killed the animals in this experiment, it is seen that thallium must be present in a high concentration in order to penetrate the cells rapidly and cause death in acute poisoning. An amount equal to one-sixth the acutely lethal dose caused death in chronic poisoning, and the onset of symptoms was slower. This seems to indicate that thallium is a cumulative poison, and low concentrations will penetrate the cell and cause death, or at least produce an alteration of cell function if sufficient time is allowed. Thallium is concentrated to a considerable

extent by the kidneys, but the total excretion of a single dose of thallium in the urine is a slow process which may last for several weeks. The elimination curves (55) have the exponential shape characteristic of substances eliminated in unit time as a fraction of the total amount of substance present at any given time. Prick et al. (29) have found thallium in the urine sixty days after the last dose. Thallium is eliminated in the feces as well as in sweat and milk. The appearance of thallium in the feces in the later stages of thallotoxicosis arises from the excretion of thallium in the bile, contamination of pancreatic secretions, and from excretion directly into the colon. Fecal elimination is reported to be the principal route in some animals, but this does not seem to be true for man. This difference appears to be a genuine species variation.

That thallium is rapidly absorbed through the skin is indicated by the occurrence of systemic poisoning after the application of depilatory creams which contain it.

Thallium accumulates to a slight degree in the skin and hair. The alopecia in thallotoxicosis is caused by the keratinizing effect of thallium upon the roots of the hair follicles (51, 52, 54). This effect does not require large amounts of thallium.

In view of the histological damage recorded in the literature, and the distribution of thallium shown in these experiments, it is no surprise that the sequelae of thallium poisoning include sensory and nervous disorders such as ataxia and choreiform movements, blindness, peripheral neuritis, and kidney damage. As stated previously, gastrointestinal disorders are present, but do not predominate over those of the nervous system.

Recuperation from thallium poisoning is slow and may require six weeks to a year. The methods of treatment presently employed are empirical and symptomatic, and generally unsatisfactory. Potassium iodide orally, followed by sodium thiosulphate intravenously have been given along with increased fluid intake, in the belief that the thallium would first be precipitated, then solubilized and washed out through the kidneys. Dimercaprol has been used, but it is not very effective since thallium has a lower tendency of forming dimercaptide compounds than some other heavy metals. Dithizone was recommended recently, but its use has caused diabetes. Thyresson (92, 93), Pastinszky (94) and Lund (56) have begun to study the influence of thallium on enzyme systems and tissue metabolism, and on the mechanisms of its excretion and detoxication. This is of great interest, and may lead the way to better methods for the treatment of thallotoxicosis.

CHAPTER V

SUMMARY

A method is presented for the determination of thallium in urine, feces, blood and tissues. It is based upon the destruction of organic material by ashing with sulphuric and nitric acids, and precipitation of the thallium as a thallium-bismuth iodide complex, $(TlI)_2.BiI_3$. The precipitate is separated by centrifuging, and is then washed, first with water and then with alcohol. The complex is oxidized with bromine in glacial acetic acid, and then sodium formate is added to form a formate-acetic acid buffer which inactivates the excess bromine. The thallium in the complex is determined by iodometric titration. Antimony, arsenic, copper, iron, lead, mercury and tin do not interfere.

The distribution of thallium in the urine, feces, blood and tissues was determined after acute poisoning by constant intravenous infusion of thallium (I), and after chronic poisoning by the daily administration of thallium (I) orally.

In the experiments designed to show acute poisoning, two dogs were infused, one at the rate of 1.75 mg. Tl^+/kg./min., and one at the rate of 1.0 mg. Tl^+/kg./min. Although the rate of thallium infusion was different, the animals died after the administration of 245 mg. Tl^+/kg./min., and 253 mg. Tl^+/kg./min., respectively.

In the experiments designed to show chronic poisoning, 5 mg. Tl^{+}/kg./day was administered orally in gelatin capsules to two dogs. These animals died on the seventh and eighth days after receiving a total amount of 35 mg. Tl^{+}/kg., and 40 mg. Tl^{+}/kg., respectively.

Thallium was found in the urine of the acutely intoxicated dogs within twenty minutes after the infusion of the thallium was started, and in the chronically intoxicated dogs, it was found in the urine from the third day until death.

Thallium was found in all organs and tissues analyzed except hair and bone in the acutely poisoned animals, and hair in the chronically poisoned animals. The more vascular organs were found to contain the largest amounts of thallium in acute poisoning. The distribution of thallium was not uniform in the chronically poisoned animals, but the range between the organs containing the most and the least amounts of thallium was not great.

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