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THE PHARMAOLOGICAL ACTION OF TIN

IN ORGANIC COMBINATION

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I N D E X.

PHARMACOLOGICAL ACTION OF TIN IN ORGANIC COMBINATION

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THE PHARMACOLOGICAL ACTION OF TIN IN ORGANIC COMBINATION.

By

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The use of tin in the various trades and industries usually in the form of "tin alloys" and the use of tin and tin "plating compounds" in the manufacture of cans, etc., for preserving food products, has made the subject of tin poisoning one of special interest. To date there has been but little reported as to the pharmacological action of tin either in organic or in inorganic combination. It was for this reason that we undertook a further study of tin and its mode of action on the body.

It has been our object in this paper to:

- (1) Briefly review the history of tin, its metallurgy and its alloys.
- (2) Outline the general pharmacological action of tin.
- (3) Summarize the clinical symptoms of tin poisoning.
- (4) Study the absorption, mode of action, and excretion of tin (more especially tin in organic combination).
- (5) Study of the pathological changes and cause of death as produced by organic tin compounds.
- (6) Comparison of the action of tin with other metals of similar groups, more especially lead, mercury, copper and magnesium, as well as with other compounds.
- (7) The economic importance of tin poisoning.
- (8) Prophylactic and curative treatment of tin poisoning.

(9) Resumé of the pharmacological action of organic tin with conclusions.

(10) Bibliography.

2. HISTORY (Discovery, etc.)

The discovery of tin dates back to prehistoric times, as far back as 2500 B.C. The tin of the Old Testament which is a translation of the Hebrew word, "Bedhil" is probably a copper tin alloy which was known in Egypt in 1600 B.C. Ancient bronze, which was an alloy of copper with tin, was employed by the Greeks for coinage up to 400 B.C. when the tin was replaced by lead. The Phoenicians were said to have brought tin from the Cassiterides, and during the Roman occupation of Britain tin was taken from Cornish to Italy; it was also obtained about the same time from Spain and Portugal. The word "stannous" (Latin for tin) was found in the writings of Pliny, but it appears first to have been used not for tin but for lead and its alloys. It was not until the fourth century of our own era that it was first applied to tin. In the Latin works of the 13th century which were translated by Geber some important properties of metallic tin are mentioned. We can see from the preceding history that tin is one of the oldest known metals and it was this metal that went to make up one of the original metals associated by the alchemists with Greek mythology. By the Greek alchemists it was termed Hermes.

3. METALLURGY OF TIN.

Tin is usually found in the form of tinstone or cassiterite (SnO_2) but occasionally it is found as tin pyritesor, which is an isomorphous mixture of the sulphides of tin, zinc, iron and copper.

Tinstone or cassiterite contains, when pure, 78 to 80% of the metal mixed with various iron compounds. This ore is found chiefly at Tipuani in Bolivia, in Siberia and in Guiana. Tinstone is also found in Saxony, Bohemia, Spain, Portugal, France, the United States, Chili, Peru, China, Japan, the Malay Peninsula, and the adjacent islands, Banca, Java, Billiton, Sumatra, and Carimon; also in New South Wales, Queensland, Western Australia, Tasmania, and some parts of Africa. The greatest quantity of tin is obtained from Cornwall, the East Indies, Australia, and Bolivia.

Pyritesor bell-metal ore, which contains tin, zinc, iron and copper as the sulphides is found at Huel Rock, St. Agnes, and Cornwall.

Tin is also found in small quantities in epidote, columbite, and tantalite, in mineral waters, and in some meteorites.

The essential reaction for obtaining tin from tinstone which represents the chief industrial method of obtaining the metal, might be written:



There are two general methods of carrying out this procedure,

(a) Extraction of tin in the dry way which involves

- (1) Pulverization of ore.
- (2) Washed to remove granite or slate.
- (3) Roasted to oxidize the sulphides of Fe and Cu, and to drive off the arsenic.

- (4) Rewashed to eliminate the sulphate of Cu and oxide of iron.
 - (5) Reduced with coal in a reverberatory furnace.
 - (6) Is remelted at a gentle heat and the pure metal flows away from compounds of iron and arsenic.
 - (7) Collection of pure tin.
- (b) Electrometallurgical Processes.

These processes have been applied to the extraction of tin from its ore and slags, but without much success. This is an expensive method and from an industrial standpoint is impractical.

The principle of this method is: A solution of the ore is made corresponding to three to five per cent sodium tannate and 12 to 15 per cent common salt. This addition of salt confers high conductivity to the solution and enables the tin to be obtained as a spongy metallic deposit when a current of 50 to 150 amperes at 2 to 3 volts is employed, with the solution at a temperature of 40° C. to 50° C.

Tin has also been refined electrolytically through the medium of a solution of sodium thio-stannate.

Commercial tin reaches a high state of purity; it seldom contains less than 99% of the metal. Although all tin has been refined, the best quality is known as refined tin. It is made from the purest ores and submitted to a lengthened process of refining. The ordinary quality of tin is cast into moulds and known as block tin. The purity of tin may be judged by melting it and casting it in an ingot mold. The ingot should be smooth, bright, and rounded; small impurities will sharpen its edges and cause it to "frost" over on solidifying, while much impurity will give the metal a yellow or purple tinge.

Grain tin is produced from refining tin by heating it to a temperature a little below its melting-point to induce crystallization and make it brittle. It is then broken by a hammer or dropped from a height. The masses thus obtained show a columnar structure. The London Metal Exchange recognizes two classes of tin: Class A containing not less than 99.75 per cent. and Class B. not less than 99 per cent. of the metal; and these official brands include the following: Straits, Australian, Banca, Billiton, English, German and Chinese.

4. Alloys of Tin.

The alloys of tin may be divided into two classes--
namely (1) Copper-Tin Alloys

(2) Tin Alloys not containing copper.

Tin-Copper Alloys. The properties of the copper-tin alloys--
the bronzes--bear no definite relation to relation to those of
their constituent metals. While tin itself is soft and fusible,
its progressive addition to copper produces the following changes:
Five per cent of tin yields a nearly copper-colored alloy which
is tough and strong and much harder than copper, so that it may be
employed for coinage and for engraving work. Ten per cent. of tin
gives a rich, yellow alloy which is still harder, so that it must be
cast; and with the addition of more tin up to 20 per cent. the alloy
becomes sonorous, though somewhat brittle, but suitable for making
small bells. With further addition of tin up to 24 per cent, an
alloy is obtained out of which the largest bells are cast; it is de-
cidedly brittle and has a grey fracture. When 33 per cent. of tin
is reached the alloy is white and constitutes the speculum metal,
and is so brittle it may be powdered in a mortar. The brittleness
continues till about 65% of tin is present, after which the hardness
diminishes as pure tin is approached.

The tin copper alloys are here summarized.

Percentage of Tin. Nature of Alloy.

- 5 Bronze for coinage and medals (a little tin often replaced by zinc), Roman nails, engineers' soft gunmetal or "brasses."
- 7 Bronze suitable for mathematical instruments.
- 8-5 Bronze suitable for wheels to be cut with teeth.
- 8-12 Soft bronze of the ancients: 9-10 per cent. for gunmetal; 10-12 per cent. for medium engineers "brasses".

Percentage of Tin. Nature of Alloy.

12-14-5	Hard bronze of the ancients, used for weapons and tools. Now used for engineers' hard bearings.
16	Soft musical bells.
18-20	Chinese gongs and cymbals.
20	Small house bells; Indian gongs.
22	Large house bells.
24	Limit for large house bells.
33	Often also a little arsenic. Speculum metal.
66	"Temper", an alloy used to harden pewter.

Bronze is hardened by a process opposite to that employed with steel. Instead of being suddenly cooled by plunging into water, it is slowly cooled to induce hardness; if suddenly cooled it becomes soft and malleable. This difference is due to the different kinds of crystals that are formed at different temperatures. Repeated hammering and cold working of bronze greatly increases its hardness. Two compounds of copper and tin are known: Cu_3Sn and Cu_4Sn . The existence of these compounds, however, is probably insufficient to account for the remarkable differences in properties between the various alloys and their constituent metals. These alloys are probably to be regarded as mixtures of one or two definite compounds with excess of a solid solution of tin in copper. The electrical properties of copper-tin alloys have been studied by Ledoux.

Bronze-bearing metals, employed for the bearings of locomotives, is an alloy composed of copper 77, tin 8, lead 15 parts. The presence of lead diminishes loss by wear and reduces local heating. The function of the tin is to provide a solvent medium for copper and lead, which do not mix well.

Phosphor-bronze is bronze containing 5 to 15 per cent. of tin and from a trace to 1.75 per cent of phosphorus, added in the form of phosphor-

tin. The phosphorus confers greater hardness, elasticity, and toughness upon the alloy. Manganese and silicon bronzes are also in vogue, but they contain little, if any, tin.

Other Tin Alloys. Tin enters into the composition of the following alloys, which contain little or no copper: common pewter, soft solder, type metal, Britannia metal, Plate-pewter, white bearing metal, and the various fusible metals. Only soft solder and common pewter will be considered here; the other alloys contain antimony or bismuth and will be discussed in Vol. XL. of this series. Tin and lead will mix in all proportions; the alloys produced are more fusible than either separate metal, and are likewise harder and tougher. There is no evidence, however, of the existence of any compound of the two metals. The lead-tin eutectic point lies at 181° C. at 24-4 atomic per cent. Pb (= 36.0 per cent. Pb. by weight). Soft solders are alloys of tin and lead in varying proportions; they occasionally contain bismuth, which lowers their melting point. The table on the previous page (Tomlinson), showing the composition of soft solders, with their melting-points, illustrates the influence of admixture upon the melting-points of metals.

Ordinary soft plumbers' and tinmen's solder is made of equal parts of tin and lead; fine tinmen's solder contains 2 parts of tin to 1 of lead.

Common Pewter. The toughest and hardest variety of pewter contains 3 parts of tin to 1 of lead; the proportion may, however, rise as high as 4 of tin to 1 of lead.

5. CLINICAL SIGNS AND SYMPTOMS OF TIN POISONING.

We may divide tin poisoning into:

(a) Inorganic Poisoning (chiefly)

1. Acute form
2. Chronic form

(b) Organic Tin Poisoning (Experimental)

The literature abounds in reports of cases of acute tin poisoning as caused by the eating of foods preserved in tin cans. There is a variance of opinion as to the amount of toxicity produced in these cases as will be related later.

There are but three cases reported of chronic tin poisoning, the most interesting being the case of Dr. Salzer reported in the J.A.M.A. 1918.

We have been unable to find any reference to cases of true organic tin poisoning and for this data we will have to rely on experimental animals.

The clinical signs and symptoms of the various forms of tin poisoning follows:

ACUTE TIN POISONING.

Under this heading we include all cases of tin poisoning, caused by the eating of foods preserved in tin. At present there is a variance of opinion as to the total toxicity of tin in foods. There are some indisputable facts in this connection which no one can deny, and which we would like to emphasize here.

Goss has shown experimentally that soluble tin compounds such as stannic ammonium chloride are capable of being absorbed by a part of the protein molecule and that this portion of the protein molecule is the last to be digested (if at all) and be taken up by the body. The relative residue left after digestion is small depending

on the length of time the protein molecule had been in contact with the tin solution. This fact with the data that the gastric and tryptic enzymes have but little action on this protein-tin complex make it quite unlikely that very toxic principles are absorbed thereby; which conclusion is applicable to food canned in tin.

This statement has been confirmed by Schryver who submitted himself to a clinical tin test. For this purpose he chose the double tartrate of tin and sodium, taking 1 grain daily for the first week--2 grains daily for the second week and three grains daily the third week, or 42 grains in all. No ill effects were felt at the end of this time and he felt (as did Lehmann) that the possibility of tin poisoning from the consumption of tinned canned goods is extremely remote. Buchanan also reports from the military camps that no epidemics of tin poisoning have occurred after the consumption of much canned (tin) goods.

Buchanan and Schryver state very definitely, however, that there is danger from the eating of canned foods where the food has been in contact with the tin plate (can) too long or in cases where the proper tin plate or soldering has not been used. The symptoms arising therefrom are from gastric irritation, oppression (lassitude), headache, nervousness, etc., going over into the chronic form of tin poisoning.

Chronic Tin Poisoning.

Dr. Salzer reported a case of chronic tin poisoning in the J.A.M.A. 1918, vol. 70. Jolles reported a similar case in 1901. In March, 1927, a case came under our observation similar to the one reported by Dr. Salzer. The following signs and symptoms as reported by Dr. Salzer and as confirmed by our own observations are typical of chronic tin poisoning--inorganic.

In two cases (one of Dr. Salzer and our own case) the cause of the poisoning was from the patient's wearing false teeth set in tin (Watt's metal which is two-thirds tin and one-third bismuth). The cause in the case reported by Dr. Tolles was the wearing of silk stockings impregnated with tin salts. All cases were confirmed as being cases of true tin poisoning (chronic) by finding tin in the patient's urine.

The symptoms, the onset of which was within a few weeks after starting to wear the metal, might be grouped as constitutional and nervous. The constitutional symptoms were those of general lassitude, weakness and a general ill feeling, while the nervous symptoms were those of chilliness or coldness in various parts of the body, headache, sleeplessness, extreme irritability and general nervousness. In Salzer's case the patient complained of indefinite pains in his legs, arms and head with soreness of the throat, resembling tonsillitis and pharyngitis. These symptoms were accompanied by a slight leucocytosis and a temperature of 102, remitting in type. In Salzer's case the symptoms persisted for some months and he felt that the nervous system suffered severely and possibly permanently. In our own case it has now been three months since she discontinued wearing her false teeth and she is not free of symptoms to date. Jolles makes no reference to the persistence of symptoms.

6. THE ABSORPTION, STORAGE AND FATE OF TIN IN THE BODY.

Previous to our experimental work with organic tin compounds the chief work that had been done on the absorption, storage, and fate of tin in the body was done by Salant, Rieger and Trenthardt who had studied this matter using inorganic tin compounds given intravenously. Salzer reports a case of tin poisoning - coming from the absorption of tin from the wearing of false teeth - (alimentary mucus membrane) as do many other workers reporting cases of acute tin poisoning -- the eating of food preserved in tin cans. Jolles reports a case of chronic tin poisoning coming from the wearing of stockings impregnated with tin.

In our laboratories we have found that soluble organic tin compounds are capable of being absorbed by way of the gastric intestinal tract - - subcutaneously, intramuscularly and intravenously. We have been able to show that the insoluble organic tin compounds are capable of absorption intraperitoneally. In all cases we have been able to find tin in the urine. In several instances we were able to detect the odor of an insoluble organic tin salt on the animal's breath after an intraperitoneal injection. After intravenous injections of soluble organic tin, we were able to detect tin in the feces, and

I. Via Gastro-Intestinal Tract.

Salant and his workers conclude that the absorption of tin from the gastro-intestinal tract may take place under certain conditions. This follows the fact that the gastro-intestinal tract is the chief source of elimination of this metal. Other workers (including Salzer) have reported cases of tin poisoning - the tin being absorbed somewhere by the alimentary mucous membrane (epithelium, etc.)

In our work we attempted to cause the absorption of both soluble and insoluble organic tin compounds and several inorganic ones - (soluble). The compounds studied were as follows: viz.

(A) Soluble

1. Di-ethyl tin bromide (organic)
2. Stannic bromide (inorganic)
3. Stannic oxide (inorganic)

(B) Insoluble.

1. Tri phenyl tin iodide (organic)
2. Tri ethyl tin hydroxide (organic)

Procedure: 200 to 300 milligrams of each of the above compounds were placed in a gelatin capsule - a mouth gag being placed on the animal - after which the capsule was placed on the posterior aspect of the animal's tongue followed by 100 cc. water to rinse the capsule down, care being taken that the animal did not expectorate the capsule. After the capsules were given the animals were watched very closely in order to note whether the drug was vomited or not. In but one case - when the di-ethyl tin bromide was given, did the animal vomit and that was some 45 minutes after the capsule had been given. In no instance was there any vomiting after the two insoluble compounds were given or after the two soluble inorganic ones. Upon careful observation we could not detect the slightest change from normal after the two insoluble organic tin compounds had been given or after one (stannic oxide) soluble inorganic salt. In the case of the stannic bromide we felt that the animal showed very mild but distinct bromide depressive symptoms within 2 hours after administration of Sn Br_4 . The urine gave a positive tin test.

In the case of the soluble di-ethyl tin bromide (organic)

the animal (dog) showed marked symptoms of poisoning within 45 minutes after administration. Vomiting and defecation occurred, the animal was very weak and trembly. Respiration was shallow and labored and the vomitus was greenish yellow in nature, similar to the gastro-intestinal contents noted after intraperitoneal injections of insoluble tin (organic) compounds.

Defecation continued for 3 to 6 hours after administration as did the periodic vomiting. Complete recovery took place 24 to 36 hours after the initial administration. The urine twenty-four hours after administration showed traces of tin which with the signs and symptoms noted above is conclusive evidence that this one organic tin salt was absorbed via dog's gastro-intestinal tract. Unfortunately we didn't have ample quantities of the other soluble organic tin compounds for similar administration.

The fact that all animals after receiving the insoluble organic tin compounds did not show any ill effects and also that the specimens of urine examined were free from tin proves that insoluble organic tin compounds are not absorbed from the gastro-intestinal tract of dogs on an initial dose. Repeated attempts were not made for lack of quantity of these compounds.

As to the two inorganic (soluble) compounds used, we feel that little or no absorption took place as we failed to find the presence of tin in the urine. These observations agree with those of Salant and his workers who failed to show the absorption of tin from the gastro-intestinal tract of dogs after these animals had received 100 to 300 milligrams tin tartrate daily for a period of three weeks. White, however, working with sodium stannous tartrate found this tin salt to be absorbed in very small amounts from the dog's gastro-intestinal tract -- which view fits with our own observation

(also urine test) of mild bromide symptoms after stannous bromide had been given.

Salant reports that the gastro-intestinal tract of rats is favorable to the absorption of tin and also that when tin in the form of double salts (as the tartrate or citrate) is given in doses of 46 milligrams daily to cats for a period of three or four days that minute amounts (1 to 3 milligrams) of tin were found in the combined urine of these animals for three or four days after administration.

Conclusions: Tin via Gastro-intestinal tract.

(1) Inorganic tin salts are probably not absorbed by way of gastro-intestinal tract of dogs and if so in very minute amounts.

(2) At least one (and probably other) organic tin compounds may be absorbed by this route and gives rise to symptoms of tin poisoning.

(3) Some salts (as double salts) of tin (citrate and tartrate) may be absorbed by way of the gastro-intestinal tract of cats and rats as shown by Salant.

(4) Dogs urine failed to show the presence of tin in all cases of insoluble organic compounds and of soluble inorganic ones, (except Sn Br_4) but gave a positive test when a soluble organic compound was administered.

II. Via Venous System. Most of our early experimental work was done on the intravenous injection of certain soluble organic tin salts -- the two chief ones being di-methyl tin bromide $(\text{CH}_3)_2 \text{SnBr}_2$ and di-ethyl tin bromide $(\text{C}_2\text{H}_5)_2 \text{SnBr}_2$. Both of these salts are very soluble and lend themselves well to intravenous injection. Our recorded data was derived largely from the intravenous use of these two salts.

Most of the previous work done on the intravenous injection of tin salts has been done by Salant, Rieger and Trenthardt who working with inorganic tin salts (sodium stannous tartrate) found that these compounds disappeared from the blood stream within two or three hours after injection and that these salts were found deposited in the skin - 25%, and in the liver -5% of the amount injected. Otherwise the deposition of tin seemed quite general. (A resumé of their experimental findings appears elsewhere.) These workers found that the elimination of these salts takes place chiefly by way of the gastro-intestinal tract -- the kidney playing but a subordinate though an important role in the elimination of tin. We share with these workers this view as to the elimination of organic tin compounds as to the kidney, but in regard to the gastro-intestinal tract we can say that it does aid in the elimination of tin but we did not carry out any quantitative analyses to determine the relative amount eliminated by the gastro-intestinal tract and kidney. Salant's view, however, is contradicted by Unger and Bodlander.

We have found using organic tin compounds (as did Salant and his co-workers using inorganic tin compounds) that the elimination of tin i.e. by any route is very slow, starting two or three days after the initial administration and lasting for some weeks.

III, Via Subcutaneous or Intramuscular Injections.

Our observations regarding the subcutaneous and intramuscular injections of organic tin compounds have been confined to one salt - - viz. di-ethyl tin bromide (C_2H_5)₂SnBr₂. For the subcutaneous or intramuscular use of this compound we used 10 to 15 cc. of a one percent aqueous solution (sterile). We noted in all cases whether the injections was made in the region of the thigh, abdominal or chest regions and either subcutaneously or intramuscularly

that within three hours an acute inflammatory reaction at the site of injection occurred. These reactions were so severe that it was impossible to give a second injection without being brutal. The reaction itself lasted from 10-14 days, after which it slowly subsided and the animal recovered. We were able to obtain positive tests for tin in the animal's urine 3 days after injection. As to the constitutional symptoms produced these seemed to be very mild in nature, which shows that the absorption by these routes must take place slowly.

IV. Via Intraperitoneal Injections.

These injections were resorted to using those compounds (organic) which were insoluble in all the ordinary solvents. It was by this method and by this method alone that we were able to study the pharmacological action of these insoluble tin salts.

Elsewhere in this paper under "The Pharmacological Action of Some Insoluble Organic Tin Compounds" we have gone into detail as to the observations and effect of such injections. Here it will suffice to briefly summarize our conclusions pertaining to intraperitoneal injections as made by us.

- (1) That absorption via intraperitoneal route does take place of insoluble organic tin compounds, is probably due in part to their powers of volatilization.

Evidence for such absorption is tin in urine and the odor of fumes on breath (mentioned later).

- (2) All signs and symptoms of acute poisoning are produced within 30 minutes after injection.
- (3) Excretion does take place by way of lungs, in at least one instance, viz. tri-ethyl tin hydroxide. The urine gave a positive test for tin after tri phenyl iodide.

(4) Death is produced within 1 to 5 hours after 800 to 900 milligrams of either salt is given, the time of death depending in part on the temperature at which the salt was given.

V. Via Skin.

Jolles has shown quite conclusively that tin may be absorbed thru the skin. The evidence as submitted by him being the finding of tin in his patient's urine, after the patient had worn stockings impregnated with tin. This patient suffered all the symptoms of chronic tin poisoning as well. In our experimental work we have performed no experiments on tin absorption thru the skin. Jolles makes no mention of other routes of elimination or storage of tin.

7. PATHOLOGY

1. Locally (At Site of Injection.)

The reaction produced at the site of injection of the soluble organic tin compounds whether the injection was made subcutaneously or intra-muscularly was of an acute inflammatory nature. This acute inflammation lasted for some eight to ten days after which it subsided -- leaving some residual tissue reaction (evidenced by hardened tissues, etc.). At no time was there any evidence of sloughing or necrosis over these areas. That absorption took place was evidenced by the detection of tin in the urine. There were signs and symptoms of general toxemia, which fact was later corroborated macroscopically at autopsy as one of a generalized systemic poisoning. No microscopical studies were made in these cases.

2. Respiratory (Inhalation)

Corresponding to the acute respiratory symptoms as mentioned before -- the pathological findings as confined to the respiratory mucous membranes (nasal of man and laryngeal and bronchial of the dog) were those of acute inflammation and congestion as evidenced by swelling and redness. This congestion was strictly local produced wholly by the irritating fumes of these organic compounds (which were probably not absorbed (or adsorbed)).

3. Intravenously (Generalized)

One compound (tri-ethyl-tin-bromide) was given intravenously for a study of symptomatology and pathology in daily doses of 15 cc. 1% aqueous solution. At the site of injection there were no signs of reaction provided the drug was "gotten" into the vein (lateral vein of dog's fore leg). If any of the solution escaped into the surrounding tissues, a reaction took place similar to the ones described under subcutaneous and intramuscular injection. At

autopsy the macroscopical picture was one of an acute systemic poisoning - - having its greatest effect on the heart muscle (causing it to be flabby) and the kidneys (signs of an acute nephritis). The intestinal mucosa appeared inflamed. There was nothing remarkable concerning other organs and tissues examined.

Microscopical Picture.

Heart. The epicardium contained a few leucocytes and the living cells show signs of mild degeneration - nuclei irregular etc. The myocardium contained much connective tissue and the muscle fibers seemed to be far apart. There was congestion around the blood vessels. The muscle fibers themselves showed irregular nuclei and the cytoplasm seemed pale and unhealthy.

Kidney. The kidney showed signs of congestion in the region of the capsule. The tubules appeared distended and were lined with swollen granular epithelium. All capillaries and blood vessels were congested and showed signs of early sclerosis.

Intestine. (Large and Small).

Both large and small intestine showed signs of degenerative mucosa- similar to sloughing with marked congestion of the intestinal wall. There was an outpouring of lymphocytes in all portions examined. Nuclei of cells appeared irregular and small as compared to cytoplasm.

Liver. Capsule was thickened and was densely fibrous and was invaded by lymphocytes and many polymorphs. In the peri portal areas there is an increase in the connective tissue elements.

Gall Bladder. Epithelial lining and wall congested.

Urinary Bladder. Degeneration of epithelial lining with underlying venous congestion.

Lung. Slight congestion mostly peri bronchial.

Brain. No remarkable findings except toxic degeneration and oedema.

Spleen. Capsule was thickened and there were some signs of toxic change with venous congestion.

4. Intraperitoneally. (Intra-abdominal)

We may divide the pathological findings thus produced into local and systemic changes produced by the intraperitoneal injections of the two insoluble organic tin compounds, viz.

(A) Local. Within 12 minutes in one instance when warm olive oil and tri-phenyl tin iodide were injected all the signs of an acute inflammatory reaction of the peritoneum were produced. In the other instances when cold olive oil was used the same phenomena occurred but late as shown at autopsy. The microscopical sections of the peritoneum corroborated these findings of acute inflammation.

(B) Systemic

Macroscopical. Because of the relatively short periods of time (few hours) elapsing between time of injection and death it was very difficult to study minutely the macroscopical changes - - however, in the intestinal tract, liver and kidneys there were evident signs of an acute toxic reaction.

Microscopical Picture. In but one case - i.e. when the tri-ethyl tin hydroxide had been given intraperitoneally and death occurred a few hours later were these microscopic sections made. The microscopic picture thus pro-

duced was rather limited -- all the pathology being limited to the peritoneum, liver, intestinal tract and lungs. A description follows:

1. Peritoneum. The peritoneum appeared congested with an outpouring of polymorphs. All blood vessels were congested. The peritoneal lining cells showed but little change either in nuclei or cytoplasm - due probably to the short time of direct exposure.
2. Liver. Capsule was thickened and showed the presence of engorged blood vessels. All the periportal areas showed some evidence of fatty degeneration of cell cytoplasm.
3. Intestinal Tract. (Stomach - Small and Large Bowel)
As stated before the stomach and intestines were filled with a heavy yellow mucus. With this mucus there was a mucoid material in the cell lining of the gut with evidence of cell degeneration and destruction. All intestinal gland cells appeared active and there were many scattered polymorphs here and there.
4. Lungs. There was a peribronchial inflammatory reaction consisting of many polymorphs - and a few lymphocytes. The lung tissue itself appeared to be normal in every way.
5. Other Organs. There were no abnormal microscopical findings in other organs, viz. heart, spleen, kidney, bladder and nervous tissue.

8. PHARMACOLOGICAL ACTION OF SOME INSOLUBLE

ORGANIC TIN COMPOUNDS.

The two organic tin compounds tri-ethyl tin hydroxide $(C_2H_5)_3SnOH$ and tri-phenyl tin iodide, $(Ph)_3SnI$ submitted to us by Dr. Kraus were found to be insoluble in all the ordinary solvents. It was for this reason that we had to resort to intraperitoneal injection of these compounds. One gram of the above salts were suspended in 20 cc. of sterile olive oil. The oil was sterilized by boiling, the salts being sterilized by washing in a weak alcoholic solution, injection taking place under aseptic conditions (sterile).

Injection No. 1. Animal: female dog. Weight: 12 kilo.

Procedure: 20 cc. of the warm olive oil was used to which was added 1 gm. of tri-ethyl tin hydroxide $(C_2H_5)_3SnOH$; fumes were given off at once but the mixture was not injected intraperitoneally until it had cooled. Time of Injection: 2:26 P.M. April 4th, 1927.

Observations. The animal at once showed signs of great pain as evidenced by howling, twitching of muscles, and frantic movements. At 2:30 vomiting occurred, the vomitus being of a greenish-yellow in color. Heart and respiration, slow and feeble. By 2:33 the animal lay prostrate on the table being unable to move and responding to no stimulation. The heart was very weak, the respiration slow and shallow. This prostration lasted until 2:38 when the animal died, 13 minutes after injection. We could not detect the odor of the salt at any time and it was impossible to obtain a specimen of the urine for a tin test.

Immediately after death an autopsy was performed which revealed a congestion of all viscera (abdominal) much frothy material in stomach and intestines and inflammation of the peritoneum. The heart, lungs and kidneys appeared normal macroscopically.

Injection No. 2. Animal: female dog. Weight: 12.5 kilo.

Procedure: 20 cc. of cold olive oil (after sterilization) was used to which was added 1 gm. of Tri-ethyl-tin hydroxide $(C_2H_5)_3SnOH$.

This suspension was injected intraperitoneally.

Time of injection: 2:05 P.M. April 4, 1927.

Observations. The animal showed some signs of pain at the time of injection due to the puncture of the abdominal wall but no signs of acute pain immediately after injection.

2:10 P.M. weakness, vomiting of green fluid. Tremors.

2:20 P.M. weakness, vomiting of green fluid. Tremors.

At this time heart was weak, respiration rapid.

2:35 pupils contracted, animal growling, showed loss of balance, and many unrelated movements.

3:05 P.M. Animal staggered as though blind, eyes retracted, walked about aimlessly, failed to drink water and could be quieted only by patting.

3:10 P.M. fumes of the salt were smelt on the breath of the animal and it was unable to walk about and lay prostrate on table. Heart was very feeble, respirations at this time very shallow and labored. Animal would not respond to stimulation of any kind.

3:25 P.M. Animal was killed 1 hour and 20 minutes after injection by means of over-etherization, in order that suffering might not be prolonged.

An autopsy was performed at once. Sections of all visceral organs being submitted to the Pathological Department for microscopic sections. Specimens of urine and gastric contents being submitted to the Chemistry Dept. for tin test. The macroscopical findings at autopsy were as follows: Acute inflammation of the visceral and parietal peritoneum. Congestion of all visceral (abdominal) organs. The

stomach and bowels were filled with greenish, yellowish froth and seemed to be in a state of contracture. The kidneys congested and the urine cloudy and thick.

Heart and lungs: Were essentially negative macroscopically.

Central nervous system was also negative macroscopically.

A report of the microscopic sections will be submitted later.

The specimens of urine and gastric contents as submitted to the Chemistry Dept. for the detection of tin were reported as probably positive, using the Longstaff method of determination, which test is said to be sensitive to 1 part to 1 million. This test is conclusive if iron is not present. However, on several previous occasions the urine has shown traces of tin after injection, which confirms the findings of other workers. As far as we know the gastric contents had not been examined heretofore.

Conclusions: From the intraperitoneal injections of this one insoluble organic tin compound we are able to draw the following conclusions:

1. Having previously tested this one insoluble tin salt tri-ethyl tin hydroxide (C_2H_5)₃SnOH in the laboratory we found that it was highly volatile at comparatively low temperature. The fumes given off were very pungent and irritating to the mucus membranes of both experimenter and experimental animal (as given intratracheally).

From the two foregoing injections we can clearly see that when the salt was given at the temperature of volatilization or below that the effect were more immediate, more pronounced and more harmful to the animal. We feel that the relative toxicity of this salt as given intraperitoneally is due in a major way to its volatility. Greater emphasis might be laid on this point because of its highly insoluble nature.

2. Excretion of this organic tin salt Tri-ethyl tin hydroxide (C_2H_5)₃

SnOH takes place through the lung (as evidenced by odor), through the kidneys (urine gives positive tin test) and probably by the way of the intestinal tract (as evidenced by a probable positive tin test in the gastric contents).

3. Tri-ethyl tin hydroxide $(C_2H_5)_3SnOH$ causes acute inflammation of all the tissues and organs with which it comes in contact as evidenced by the signs of acute inflammation both macroscopically and microscopically.

4. Cause of death due to this salt is respiratory failure with secondary myocardial failure due to toxicity, probably volatile by way of the blood stream.

5. From a practical standpoint we could say that this salt represents one high in toxicity and because of its volatile nature would necessarily be dangerous to use commercially or therapeutically.

Injection No. 3. Animal: male dog, weighing 11 kilo. Procedure: 25 cc. sterile olive oil to which was added 1 gram triphenyl tin iodide Ph_3SnI was injected intraperitoneally. Time: 2:20 P.M. April 27, 1927.

Observations: The animal at once showed evidence of pain and ten minutes after the injection was given defecation and vomiting occurred. By 2:50 P.M. the animal was very weak and dyspnoea. This weakness and difficulty in breathing continued for four hours and a half, when the prostration ended in death. The autopsy findings were much the same as were noted under tri-ethyl tin hydroxide given intraperitoneally. No microscopic sections were taken and fortunately a specimen of the urine was obtained which gave a positive tin test. It was to be noted also that at no time could the odor of this tin compound be detected on the animal's breath. This is not surprising in view of the fact that this compound volatilizes with difficulty as compared with the relative ease with which tri-ethyl tin hydroxide

volatilizes.

Conclusions:

1. From the foregoing we are able to conclude that both insoluble organic tin salts tri-ethyl tin hydroxide $(C_2H_5)_3SnOH$ and tri-phenyl tin iodide $(Ph)_3SnI$ produced death when given in sterile olive oil intraperitoneally.
2. Absorption of these compounds occurred as evidenced by detection of tin in the urine and the detection of the odor of one compound tri-ethyl tin hydroxide on the breath of the animal.
3. Excretion of these insoluble organic tin compounds takes place through the lungs and kidneys.
4. Cause of death. Respiratory failure with secondary myocardial involvement.
5. In order of toxicity the tri-ethyl tin hydroxide is much more toxic than is tri-phenyl tin iodide.

Pharmacological Action of Some Insoluble Inorganic Tin Compounds
as Given by Mouth.

The two organic tin compounds tri-ethyl tin hydroxide $(C_2H_5)_3SnOH$ and tri-phenyl tin iodide $(Ph)_3SnI$ were found to be very insoluble in all the ordinary salts. In order to test the pharmacological action of these salts we gave 2 grs. of tri-ethyl tin-hydroxide to one dog and 2 grs. of tri-phenyl tin iodide to another dog in gelatin capsules. Both dogs retained the capsules for one hour after which one dog having been given the tri-phenyl tin iodide vomited. The capsule could not be found in the vomitus but it is quite likely that it had dissolved and the salt had spread through the stomach contents. Neither animal appeared ill and suffered no ill effects at any time thereafter. Both were kept in separate cages for a period of ten days during which time they were carefully watched for signs and symptoms of tin poisoning. At no time did either dog show such signs and at the end of this time both were used for class purposes, and from a macroscopically survey of the organs after death all seemed negative.

Conclusions: We could conclude from the small series of experiments that organic tin compounds (insoluble) are inert when given by mouth and produce no signs or symptoms of tin poisoning.

It has been found by some workers that tin compounds do produce signs of nausea and vomiting which bears out our work with the phenyl-tin iodide which did cause vomiting one hour after injection.

The fact that tin compounds are inert, or relatively so, when given by mouth is of much economic importance, and lowers much the danger of acute tin poisoning. It is highly probable, however, that when given over long periods of time (as shown by Salzer) that signs and symptoms

of chronic tin poisoning do occur which bear out our findings when insoluble compounds were given intraperitoneally.

9a. PREPARATION OF COMPOUNDS.

We are indebted to Dr. Kraus and his associates of Brown University for their kindness in submitting to us five organic tin compounds that we might study the pharmacological aspects of organic tin.

These compounds were:

- (1) Di-methyl tin bromide $(\text{CH}_3)_2\text{SnBr}_2$ soluble.
- (2) Tri-methyl tin bromide $(\text{CH}_3)_3\text{Sn Br}$ soluble.
- (3) Di-ethyl tin bromide $(\text{C}_2\text{H}_5)_2\text{Sn Br}_2$ soluble.
- (4) Tri-phenyl tin iodide $(\text{Ph})_3\text{Sn I}$ insoluble.
- (5) Tri-ethyl tin hydroxide $(\text{C}_2\text{H}_5)_3\text{Sn OH}$ insoluble.

For the method of preparation of these compounds we refer to the various articles published by Dr. Kraus and his associates in the Journal of the American Chemical Society.

Also:

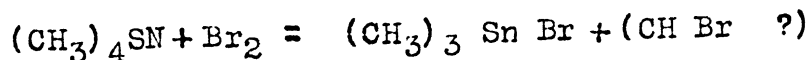
- (6) Other Organic Compounds as prepared in our own laboratory.

Details of preparation of all compounds follows:

(1) Di-methyl Tin (di) Bromide: The preparation of this compound according to Kraus and Greer (J. Amer. Chem. Soc. 47-2568, 1925) is as follows:

The dibromide is readily prepared by further brominating tri-methyl tin bromide. This is done by slowly dropping an equivalent quantity of bromine into trimethyltin bromide while the temperature is gradually raised from 50° to 80° . Sunlight is preferably excluded. The crude product of bromination is freed from monobromide by washing with petroleum ether. Dimethyltin dibromide melts at 76° .

(2) Trimethyl Tin Bromide: This compound may be made by brominating tetra methyl tin according to the reaction:



According to Kraus and Sessions (J. Amer. Chem. Soc. 47-2361 (1925))

the method of preparation is as follows:

The calculated amount of bromide (2 atoms of bromide per atom of tin) as allowed to drop slowly into tetramethyl tin in a distilling flask, cooled to a temperature of about 10°. When the required amount of bromide has been introduced the mixture is allowed to come to room temperature and the produce is purified by fractional distillation and crystallization. A small amount of dimethyl tin dibromide is formed, while a corresponding amount of tetramethyl tin remains unchanged. There is little loss of tin compound if the lower- and higher-boiling fractions are preserved and worked over. Trimethyl tin bromide melts at 27° and boils at 165°. Its purity is readily recognized by the sharpness of its melting point.

(3) Di ethyl Tin Di Bromide: Diethyl tin dibromide is prepared by brominating triethyl tin bromide with free bromine in carbon tetrachloride solution. After fractional crystallization, preferably under vacuum, the product is purified by fractional crystallization from organic solvents such as benzene, by washing with low boiling petroleum ether.

(4) Tri-phenyl Tin Iodide:

As a starting material for the making of this compound tetraphenyl tin was used. This preparation (tetra phenyl tin) may be prepared by one of two methods, viz. method as used by Polis or by means of zinc diphenyl. These two processes are as follows:

(A) Sodium-tin Alloy Method:- (Polis) Bromobenzene was refluxed with about four times the calculated quantity of a 14% sodium-tin alloy on an oil-bath for 12 hours. The resulting gray solid mass was treated with cold carbon tetrachloride to remove unchanged bromobenzene, and then repeatedly extracted with boiling carbon tetrachlor-

ide or benzene. The tetraphenyl tin so obtained melted at 225-226° after one recrystallization; yield, about 50%.

(B) Zinc Diphenyl Method: A quantity of phenylmagnesium bromide was prepared in the usual way in a 3-necked boiling flask, provided with a reflux condenser fitted with a calcium chloride tube, a dropping funnel and a tube through which a current of nitrogen could be introduced. On completion of the reaction a suspension of dry zinc chloride in absolute ether was added through the dropping funnel. Reaction took place immediately. Toluene was then added and the ether distilled on a water-bath. To the cooled solution was added a solution of an equivalent amount of stannic chloride in toluene and the mixture boiled for one hour. All of these manipulations were carried out in an atmosphere of nitrogen. After cooling, dilute hydrochloric acid was added and the solution filtered. The residue was extracted with boiling benzene. The toluene layer of the filtrate was united with the benzene extracts and the mixture concentrated and cooled; yield, 91, 2%; m.p., 224-225°.

After the tri-phenyl has been prepared and purified the following procedure is carried out to obtain the triphenyl tin iodide in pure form. This compound as made by Dr. Kraus was prepared by the action of iodine on tetra-phenyl tin. This is contrary to Polis view (Polis Bev. 22, 2915, 1889) who states that iodine has no effect upon tetra-phenyl tin.

The preparation of the tri-phenyl tin iodide as made by Dr. Kraus follows the general plan of preparing tri-phenyl tin bromide -- the principle of which is that when a solution of tetra-phenyl tin in chloroform is treated with bromide, two phenyl groups are replaced by bromide. The technique is as follows:

To 150 g. of tetraphenyl tin, in a 150 cc. distilling flask

provided with a reflux condenser and having the side arm closed with a stopper, was added 975 g. of chloroform and the mixture boiled while 90 g. of iodine was added in small portions. After each addition of iodide the solution immediately became decolorized, until near the end, when a brown color appeared which was not discharged after boiling for one hour. The chloroform was distilled on a water-bath. The iodobenzene which was formed in the reaction was removed by distilling under a pressure of 13 mm. The residue, consisting of crude tri-phenyl tin iodide, was dissolved in ether and filtered to remove unchanged tetra-phenyl tin. The ether solution was shaken in a separatory funnel with three portions of 30% sodium hydroxide solution and the layers were separated. The ether layer, containing tri-phenyl tin hydroxide, was shaken with concentrated hydrobromic acid, the layers were separated and the ether layer was dried over sodium sulfate. On concentration of the ether solution 86 g. of tri-phenyl tin bromide was obtained which, after recrystallization from ether, melted sharply at 120-121°, yield about 50%.

(5) Tri-ethyl Tin Hydroxide: The following is the method of preparation of tri-ethyl tin bromide as used by Dr. Kraus. The hydroxide is prepared in much the same way (see literature) or by treating the bromide with a strong alkali. Tri-ethyl tin bromide is prepared as follows: Tetra-ethyl tin is treated directly with bromine in the cold, adding the bromine drop by drop or by treating a carbon tetrachloride solution of tetra-ethyl tin with bromine at ordinary temperatures. The work is purified by fractional distillation. The pure compound melts at about 27°.

(6) Other Organic Tin Compounds:

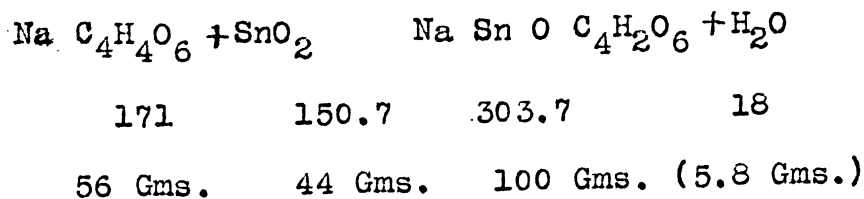
In our own laboratories we prepared two organic tin compounds, viz. (A) Sodium Tin Bromide and (B) Sodium Tin Tartrate

(not a true tartrate). The method of preparation of each is quite simple -- method follows:

(A) Sodium Tin Tartrate.

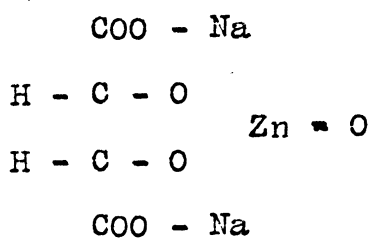
This compound is made by the interaction of sodium tartrate $\text{Na C}_4\text{H}_4\text{O}_6$ and tin (stannic oxide SnO_2 with the splitting off of water.

Reaction is:



Under each salt(or compound) is represented the molecular formula. (first line). Below (second line) is indicated the number of grams of the two salts necessary to make 100 gms. sodium tin tartrate. The various amounts were dissolved in water 100 cc. mixed and boiled for 60 minutes after which they were filtered -- the filtrate standing until the salt sodium tin tartrate settled out. No method of purification is necessary.

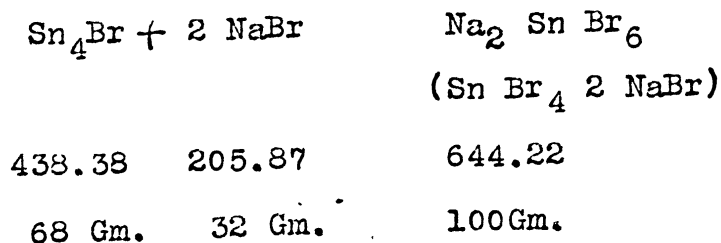
The structural formula



shows that this compound is not a true tartrate.

(B) Sodium Tin Bromide.

The preparation of this compound represents an addition (chemical) between tin(stannic) bromide (Sn Br_4) and sodium bromide (NaBr) as follows:



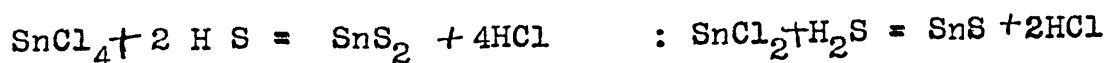
The abbreviated structural formula for sodium tin bromide is indicated above showing that this compound is merely an addition of tin bromide and sodium bromide and giving a weak combination which is reversible. The molecular weights of each compound is indicated beneath the various formulae and the various equivalents to make 100 Gms. sodium tin bromide is given on the next line.

The method of preparation is simple. The relative amounts of tin bromide and sodium bromide are dissolved in 100 cc. water, mixed, then boiled for 60 minutes after which the solution is filtered. The filtrate is allowed to stand until the compound Na_2SnBr_6 settles out or until evaporation occurs.

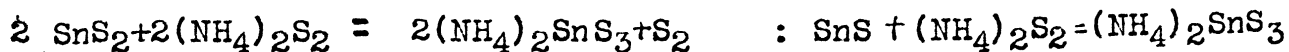
9b. ANALYSIS FOR TIN - TESTS FOR TIN.

Digest 10 cc. of urine with 5 cc. conc. HCl and small amount of KClO₃; add more HCl and KClO₃ as digestion progresses. When digestion is complete the solution is a very pale yellow; it is then diluted to 100 cc. and neutralized so that it is just slightly acid. pass in H₂S. Filter.

The solution is warmed before treating with H₂S and heated almost to boiling before filtering.

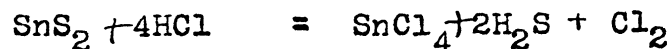
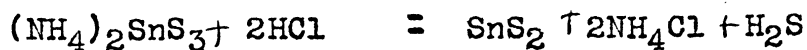


Test filtrate with more H₂S. Wash ppt. with hot water, containing a little HCl. Wash ppt. into test tube with small amount of water and add yellow ammonium sulfide (NH₄)₂S_x. Digest for several minutes with warming.



The ppt. is filtered, washed first with (NH₄)₂S_x and then with hot water. The filtrate, containing the tin, is acidified with HCl.

Tin ppts. and then redissolves.



Boil off the H₂S.

Treat with Zn and HCl - tin is deposited.

Dissolve with HCl and test.

9. DATA

Controls.

3 samp's. of own urine tested first

1. normal

2. with SnO₂ added

3. " FeCl₂ gave correct results

#2 only one which gave positive tests

Tests.

Samples Tested

as on tube

- - - - -

#1 -- urine -- tin present after (C₂H₅)₃ SnBr intravenous

#2 -- " -- " absent before (C₂H₅)₃ SnBr mouth

#3 -- " -- " present SnBr₄ mouth

#4 -- " -- " present (Ph)₃ SnBr by mouth

#5 -- " -- " SnO₂ mouth

#6 gastric contents -- tin absent after (C₂H₅)₃ SnBr intravenously

#7 blank -- own urine -- tin absent.

All samples, after the qualitative separation, were tested with both ammoniacal AgNO₃ and Ammonium Molybdate reagent.

Both of these tests agreed in all cases.

Examined May 13-16, 1927

Warren H. Reinhart.

Note: April 10th, 1927, examination of urine and gastric contents after (PH)₃ SnI was given intraperitoneally showed the probable presence of tin.

Examination of urine after intravenous injection of (CH₃)₂ SnBr showed the presence of tin test made April 6th, 1927.

The latter three tests were made by B.C. Brunstetter using the method of Longstaff.

REPORT ON DETECTION OF TIN IN URINE AND STOMACH OF DOG

TREATED WITH ORGANIC TIN COMPOUND.

The tube containing the urine was unfortunately broken, and the contents spilled on the laboratory desk. The liquid was at once taken up with a blotter. (No work had been done using tin compounds on that desk.)

The blotter was extracted with 10 cc. of dilute HCl. The volume of the extract obtained was 7 cc.

The stomach contents were divided into parts: I = supernatant liquid - 1.8 cc. - deeply tinged with hemoglobin. (On adding HCl, dense white fumes occurred; the presence of ammonia is indicated); II = sediment.

In the fourth tube 10 cc. of the analyst's urine was obtained. (It should be mentioned that about 3 hours before, part of the breakfast eaten contained canned milk.)

Tube No.	Contents	Final Color Produced.
1	Supernatant liquid of stomach: 1.8 cc.	Light blue
2	Sediment from stomach fluid	Deeper blue
3.	7 cc. of dog urine	Light blue
4.	10 cc. of normal human urine	Dark blue

After adding 1.5 cc. of concentrated HCl, and 0.5 gm. of Zn to each tube, they were placed in boiling water for 55 minutes. Each tube was then filtered into 1 cc. of saturated ammonium molybdate. They were then centrifuged and compared with regard to color.

As far as I know, the only substance in normal urine capable of giving, by direct reduction of ammonium molybdate in acid solution, a blue color, is iron. The iron content of normal urine

according to different investigators probably does not average more than 0.001 gm. per day. If one day's passage of urine is 1000 cc., 10 cc. then would be 0.000,01 g. 10 cc. of my urine were evaporated, incinerated, taken up with HCl, diluted, divided into two parts. The test for iron by (a) ammonium thiocyanate and (b) by potassium ferrocyanide was positive. Thus in the dog urine the blue color could have been produced by iron.

Red blood cells laked, then reduced by $(\text{NH}_4)_2\text{S}$, powerfully and directly reduces ammonium molybdate. This indicates that the iron in hemoglobin actively reduces ammonium molybdate, and hence the test for tin in the stomach contents is rendered doubtful.

Tin was probably present in the urine and stomach contents of the specimen examined.

This method is of use only when iron has been removed.

A better test for tin, probably, is given in Sutton's Volumetric Analysis, page 346.

Byron Brunstetter.

REPORT ON DETECTION OF TIN IN DOG URINE

Urine from a dog treated with an organic tin compound was received March 31, 1926. It was stored in the ice-box. When analyzed on April 6, 1926, a marked decomposition odor, and a cloudy precipitate of phosphates were noted.

The qualitative analytical method used was proposed by Longstaff (1) and studied for optimum conditions by Curtmann and Mosher (2). It said to be sensitive to 1 part in 1,000,000.

The procedure as adapted to urine consisted of the following steps:-

1. Filter 10 cc. of urine.
2. Add 1.5 cc. of conc. HCl to filtrate.
3. Add 0.5 gram of C.P. granular Zn; place in boiling water bath.
4. After reducing 0.5 - 1.0 hour, add 1.0 cc. conc. HCl to dissolve any spongy tin present.
5. Cool and filter into 1.0 cc. of saturated ammonium molybdate solution. (Run blank simultaneously thru the same procedure.)
6. Centrifuge and compare color with control. The blank or control used in this analysis was 10 cc. of fresh human urine. The color developed in the control was greenish blue; the color of the dog urine was a deep blue, indicating the presence of tin.

During the reduction, the color of the urinary pigment disappears. With the dog urine, on reducing an excessive foaming occurs, due to CO₂ evolution: to prevent loss of the solution, this foam is caught in another test tube, and later added to the first tube.

Summary: The dog urine analyzed contained tin.

B.C. Brunstetter.

References:

- (1) Longstaff: Chem. News. 80, 282.
- (2) Curtman and Mosher, J.A.C.S. 35, 357, 1913.

10. EXPERIMENTAL DATA

The following data as submitted by us concerning the action of organic tin compounds on the experimental animal (dog) was recorded while the animal was fully anesthetized. The aqueous injections were given intravenously in strengths of 1 to 75 and 1% (1 to 100) solution. These injections were given in the right or left femoral veins after having all recording apparatus in place, ready for action.

For the most part we have not given details as to methods of recording findings but refer to Jackson's "Experimental Pharmacology" as methods outlined in this treatise are the same as those used in this laboratory.

On the following pages we list the organic and inorganic tin compounds used in our experiments and in each case give the relative amounts of tin present.

An explanation of every finding recorded is given on the page following each figure.

FIGURE 1.

EFFECT OF GRADED DOSES OF TRI METHYL TIN BROMIDE ON RESPIR-
ATION AND BLOOD PRESSURE.

1. Blood Pressure.

The effect of this compound on blood pressure may be summarized as follows:

- (1) No change in pressure or a very slight elevation in pressure (due probably to volume injection) using a very small dose.
- (2) Slight rise above normal - when a larger dose is given (due probably to volume injection) followed by a quick return to normal.
- (3) Slight rise (due probably to volume injection) followed by a lowering in pressure as the size dose is increased.

This secondary lowering is due we believe to two factors:

- 1- Stimulation of Vagus - Centrally and peripherally

(This is variable).

- 2- Direct depressant action on heart muscle.

Evidence for two above conclusions will be submitted later.

2. Respiration.

We may classify changes in respiration as follows:

- (1) Small dose - no change.
- (2) Larger dose - slight increase in rate and depth not followed by depression.
- (3) Large dose - 3 findings, viz.
 - (a) Primary depression - often to temporary stoppage.
 - (b) Secondary stimulation - increase in depth and rate.

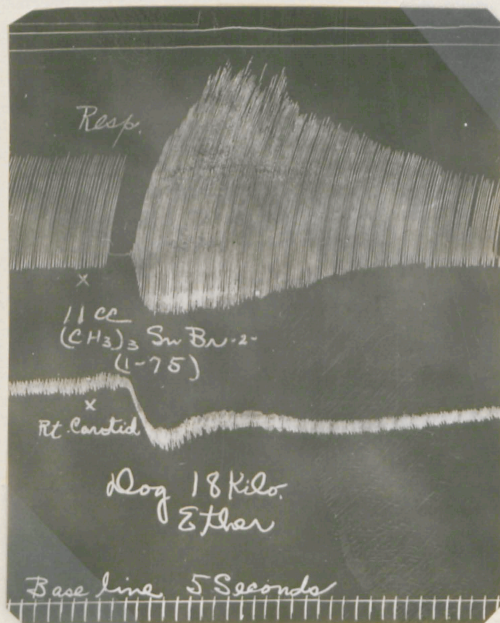


Fig. 2.

FIGURE 2.

TYPICAL RESPIRATORY EFFECT.

Herewith is shown the typical effect of tri-methyl tin bromide in a relative large dose on respiration viz. first a complete stoppage - followed by a heavy increase over normal in rate and depth to be followed in turn by a diminution in rate and depth - often to death if respiratory stimulants are not given. We explain this on the basis of a primary depression (stoppage) of the respiratory center - followed by marked stimulation (of center) and to be followed a second time by a gradual diminution (in activity) of the center.

The effect on blood pressure is the same as was noted before in Figure 1.

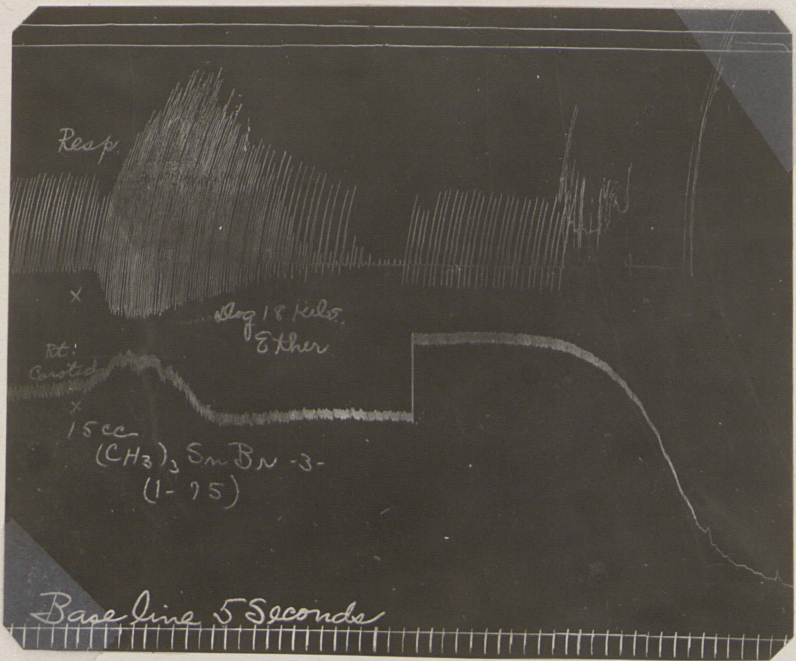


Fig 3.

FIGURE 3.

RESPIRATORY ACTION WITH FAILURE LATER AFTER TRI-METHYL TIN BROMIDE

Action of tri methyl tin bromide (third injection) on respiration (typical) and blood pressure (typical). After this action the drum was stopped for some 30 minutes during which interval the blood pressure rose and the breathing became better. The drum was now started - the respiration to stop first and followed by a sudden drop in blood pressure and an inevitable death. We explain this death on latent toxicity - which cannot be remedied.

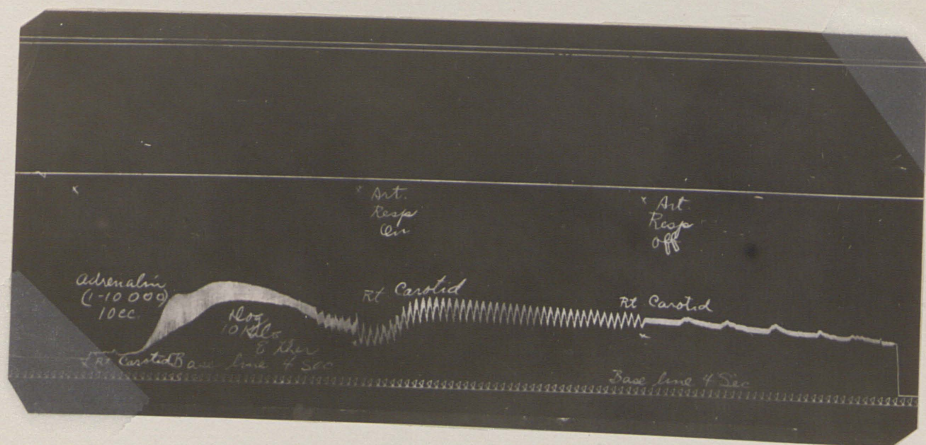


Fig. 4.

FIGURE 4.

HEART ACTION AFTER RESPIRATION FAILS.

Figure 4 shows the heart action after all respiratory movements have ceased - the animal being kept alive for a short time by means of artificial respiration. Previous to this section of record the animal (dog) was almost "gone", the cause of which was tri methyl tin bromide 12 cc. (1-75 sol.). Adrenalin in a large dose 10 cc. (1-10000) and artificial respiration was then resorted to. For a time the heart action continued only to fail later when artificial respiration was stopped. We submit this tracing to show that respiration fails before heart action.

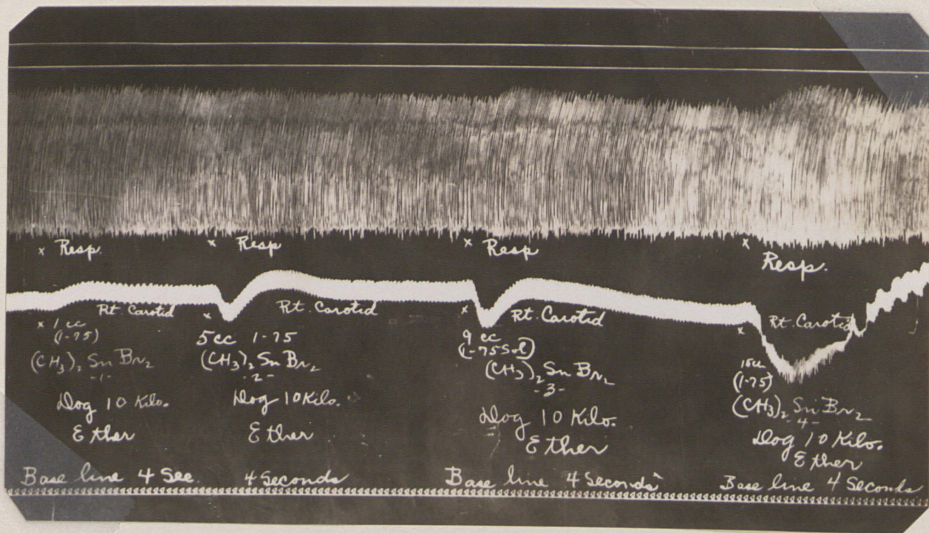


Fig. 5.

FIGURE 5.

EFFECT OF GRADFD DOSES OF DI-METHYL TIN BROMIDE ON RESPIRATION
AND BLOOD PRESSURE.

This experiment is similar to experiment No. 1, using tri-methyl tin bromide. In many respects the action recorded here is the same as was recorded using small doses of tri-methyl tin bromide as both fail to produce changes in respiration and blood pressure.

With increasing doses the same effects are shown on blood pressure and respiration as in Experiment No. 1 using the tri-methyl compound. For an explanation of this data we refer to notes concerning Figure 1.

We feel that while the action and seat of action were the same in both cases that the di-methyl tin bromide was less active than was the tri-methyl tin bromide. We rather expect this as the relative amounts of tin in the two instances may be represented by the ratio Di-methyl to Tri-methyl as .38 to .48.

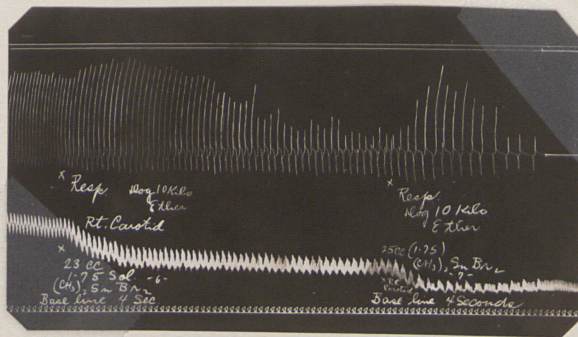


Fig. 6.

Figure 6.

STIMULATION AND RESPIRATION NEAR DEATH. DI-METHYL TIN BROMIDE.

This figure shows the effect of large doses of di-methyl tin bromide on respiration when the respiration was weak - slow and quite labored - as the animal was near death. As shown there is a decrease in rate but an increase in depth to a point near death.

This is proof that the respiratory center has still some power (ability) to be stimulated when the animal is near death - i.e. when respiration has almost ceased.

The blood pressure fell slightly at each succeeding injection - to zero at death. This further drop at each injection is quite typical of the effect of this compound.

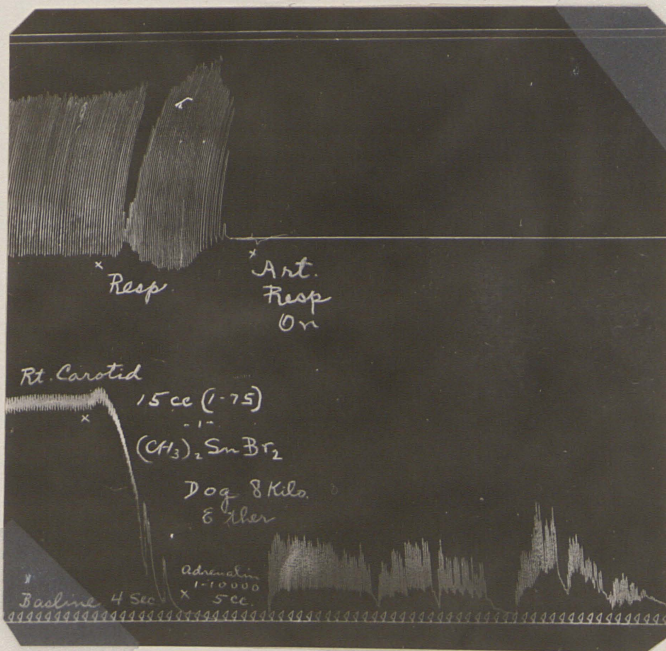


Fig. 7.

Figure 7.

DEATH AFTER AN INITIAL SMALL DOSE OF TRI-METHYL TIN BROMIDE.

We have observed in some cases (relatively few) that a small initial dose of any of these organic tin compounds will produce death - no matter what restoratives are used. This figure shows such a case - after a small dose of tri-methyl tin bromide had been given to a fresh dog. Artificial respiration, adrenalin (in large doses) and heart massage failed to revive the animal.

We explain this phenomenon on the basis of an idiosyncrasy for this tin compound.

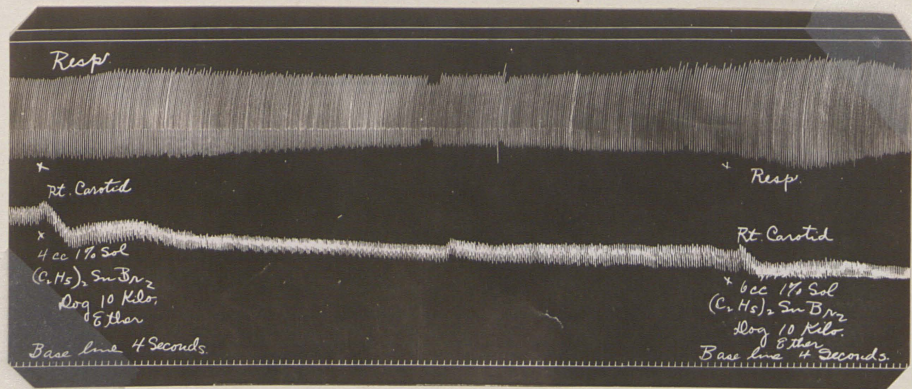


Fig. 8.

FIGURE 8.

EFFECT OF GRADED DOSES OF DI-ETHYL TIN BROMIDE ON RESPIRATION AND BLOOD PRESSURE WITH A COMPARISON OF THE RELATIVE ACTIVITY OF TRI-METHYL, DI METHYL AND DI ETHYL TIN BROMIDE.

Respiration and blood pressure are recorded here - showing the action of a small and a large dose of di ethyl tin bromide.

Respiration was very slightly altered on an initial small dose of this compound. On second injection there was a slight increase in depth and rate of breathing - but not such a marked effect as was noted by similar sized doses of di methyl or tri methyl tin bromide.

Blood Pressure was affected in the usual way - a slight elevation (due to volume injected) followed by a fall - but this action was not so marked as when the two previous compounds had been given in same dose.

Comparison Relative amounts of tin present may be represented numerically as follows:

Tri-methyl Tin Bromide	.48
Di-methyl Tin Bromide	.38
Di-Ethyl Tin Bromide	.35

This agrees with the degree of activity shown as di-methyl tin bromide showed less signs of activity than did Tri-methyl tin bromide - so Di-Ethyl tin Bromide shows less activity than even the Di-methyl Tin Bromide. We feel, however, that the mode and seat of action in the 3 cases to be same - the chief difference being in degree of activity (probably only).

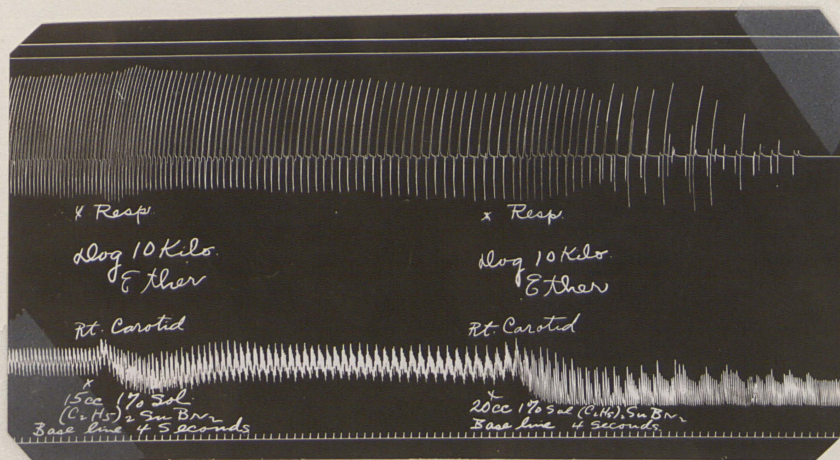


Fig. 9.

Figure 9.

EFFECT OF LARGE DOSES OF DI ETHYL TIN BROMIDE WHEN ANIMAL IS
NEAR DEATH.

In this experiment large doses of this tin compound were given to a dog - when the animal was near death. This action is comparable to action recorded in Figure 6 - after large amounts of di-methyl tin bromide had been given shortly before death.

While the action in the two instances is the same we feel that the di-methyl compound to be the stronger (in action).

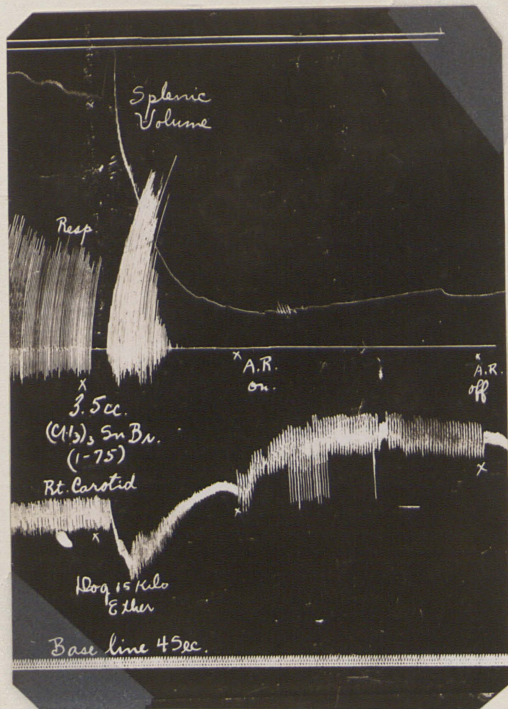


Fig. 10

Figure 10.

SPLenic VOLUME AFTER TRI METHYL TIN BROMIDE.

In this experiment there was a marked diminution in splenic volume simultaneous with a lowering of the blood pressure. This splenic contraction produced a later rise in blood pressure. Explanation of this splenic contraction may be made on the basis of vaso-motor stimulation in medulla and cord.

The effect on respiration is typical - to be followed by respiratory failure later even though artificial respiration was resorted to. Blood pressure fell and the animal died - simultaneous with the contraction of the spleen - other organs probably showed a like phenomena.

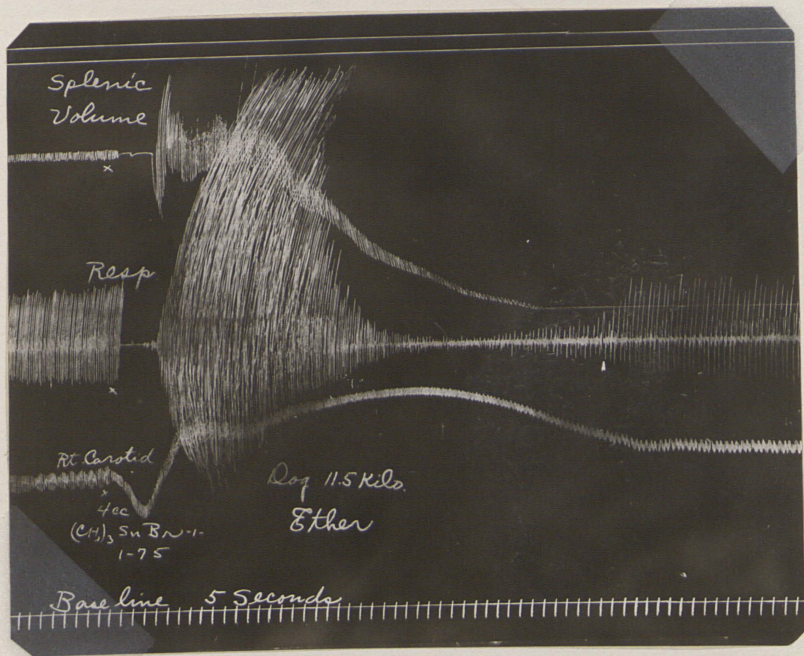


Fig. 11.

Figure 11.

SPLENIC VOLUME AFTER TRI METHYL TIN BROMIDE

For the explanation of action here see note concerning Figure 10. The effect as shown here on respiration is quite typical and very marked. Explanation has been given of this in note - regarding Figure 1.

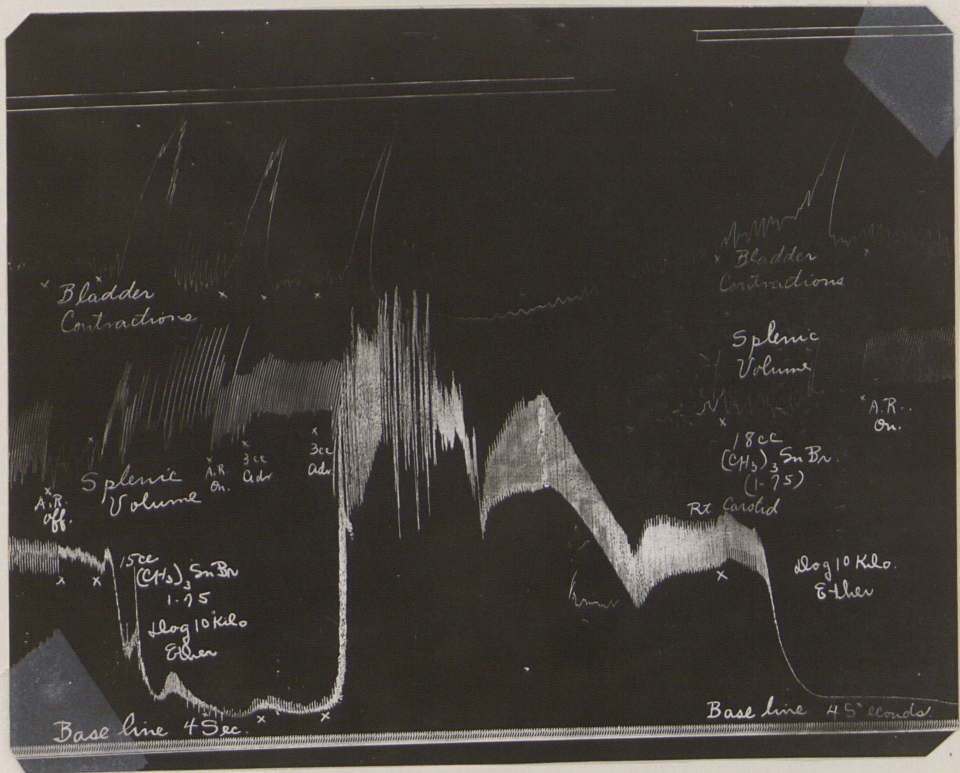


Fig. 12.

Figure 12.

BLADDER CONTRACTIONS USING TRI METHYL TIN BROMIDE

This figure shows the action of tri methyl tin bromide on the bladder. Here is shown three bladder contractions after the first injection of tri methyl tin bromide - this action being due to nerve bladder stimulation or to secondary asphyxia. Further evidence in favor of asphyxia is recorded when the second injection was given - when no bladder contraction was recorded until the blood pressure had fallen to zero. We feel here (as we recorded before) that adrenalin has a more pronounced effect after alkyl tin bromide compounds than before.

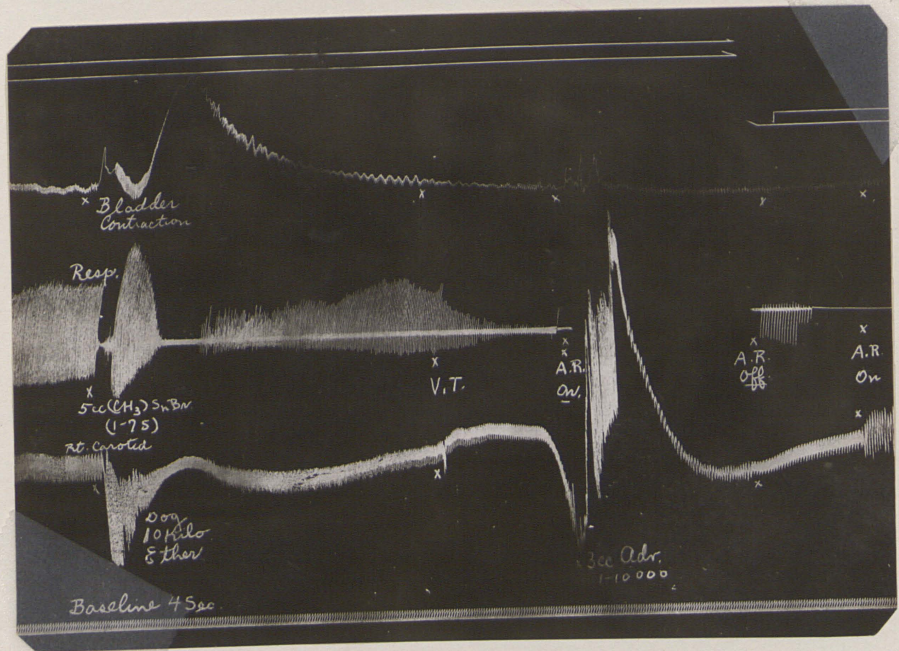


Fig. 13.

Figure 13.

BLADDER CONTRACTIONS AFTER TRI METHYL TIN BROMIDE

We feel sure in this case that the one bladder contraction recorded was due to asphyxia - a further proof over data submitted in Figure 12.

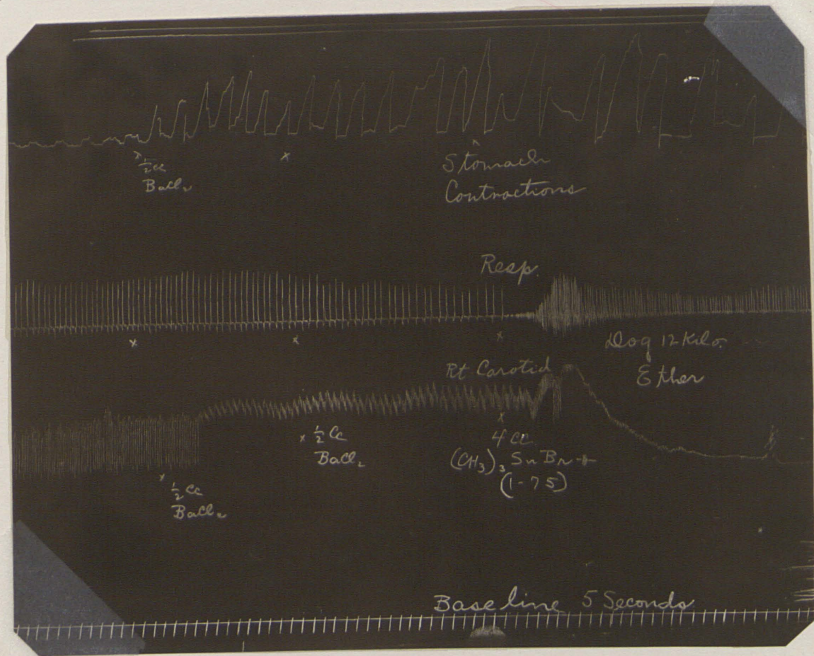


Fig. 14.

Figure 14.

STOMACH CONTRACTIONS AFTER TRI METHYL TIN BROMIDE

In this experiment the stomach contractions were aroused by the previous use of Barium ($BaCl_2$). We could detect no change in contraction after this compound had been given. We have no additional data, however, to submit in proof of this.

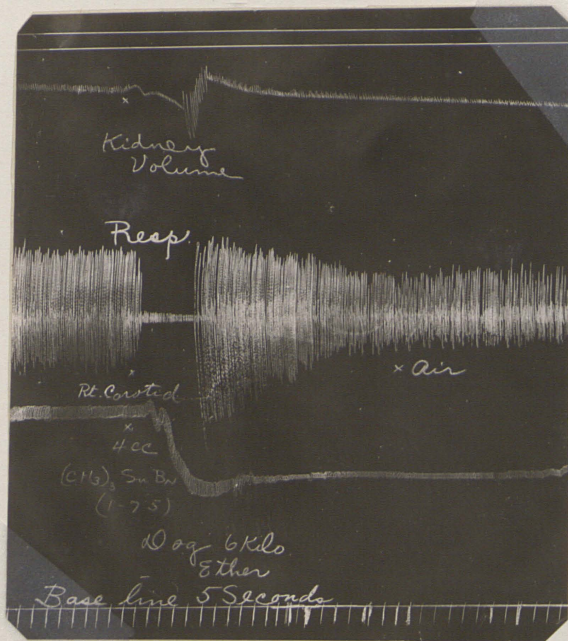


Fig. 15.

Figure 15.

KIDNEY VOLUME AFTER TRI METHYL TIN BROMIDE.

We refer to the phenomena occurring in splenic volume as shown in Figure 9 and 10. While there is not such a marked change (contraction and diminution in size) produced in the kidney volume there is a pronounced one. Our explanation of this phenomenon is that it is central-vaso motor and is simultaneous with other organs - evidence which we submit in spleen and kidney changes.

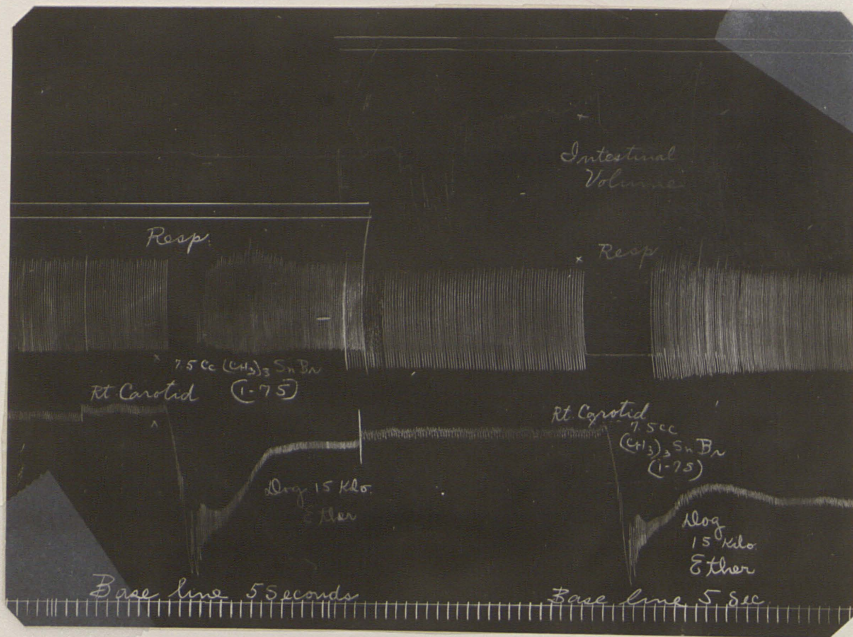


Fig. 16.

Figure 16.

INTESTINAL VOLUME AFTER TRI METHYL TIN BROMIDE.

Herewith is shown the action of tri methyl tin bromide on respiration, blood pressure and intestinal volume. As far as we could determine there was no change in intestinal volume (shown poorly here). Respiration ceased for a time when each (7.5 cc. 1-75 sol.) injection was given - the second injection being as pronounced in effect as the first. The effect on blood pressure was likewise the same.

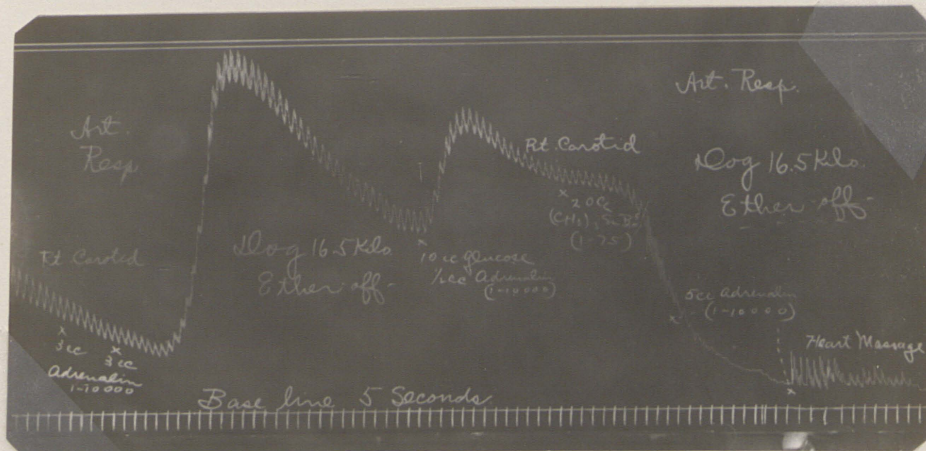


Fig. 17.

Figure 17.

INCREASED ACTIVITY OF ADRENALIN AFTER ORGANIC TIN.

This figure shows the action of adrenalin after tri methyl tin bromide. This action is much more pronounced after organic tin than before its injection. In another figure (figure) when respiration had ceased and injection of adrenalin showed remarkable power of bringing the animal back (for a time at least) when other similar drugs would probably have failed.

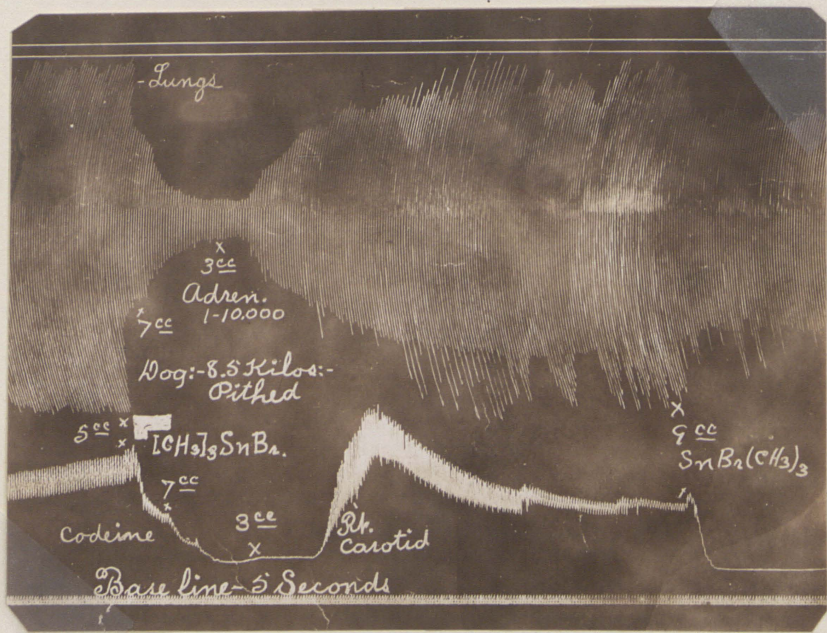


Fig. 18.

Figure 18.

LUNG VOLUME USING TRI METHYL TIN BROMIDE.

Figure 18 shows the effect of tri methyl tin bromide on lung volume. A marked constriction (a decrease in volume) occurred after an initial dose of codeine was given. Followed by an injection of tri methyl tin bromide dilatation failed to occur (probably a slight additional constriction instead). Adrenalin, however, caused the usual dilatation after the tin compound.

Another injection of tri methyl tin bromide (not preceded by codeine) produced a very slight constriction - and incidently death to the animal.

FIGURE 19.

LUNG VOLUME USING TRI METHYL TIN BROMIDE.

In this experiment increasing doses of tri methyl tin bromide was given. There was, in no case, a marked effect - merely a slight (probably) diminution in lung volume. No drugs preceded this action as did so in Fig. 18.

The changes in the blood pressure follow the general rule of blood pressure changes recorded elsewhere. The effect here is similar to that recorded in Fig. 18.

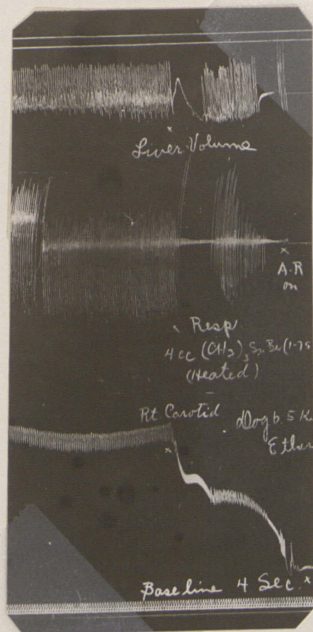


Fig. 20

FIGURE 20.

LIVER VOLUME AFTER TRI METHYL TIN BROMIDE.

By placing a liver oncometer on the left lobe of the liver we were able to study changes in liver volume. We could detect no change in liver volume when tri methyl tin bromide was given intravenously in moderately sized doses. We are in need of further proof for the above observation, however, as we are not sure that this holds in all cases.

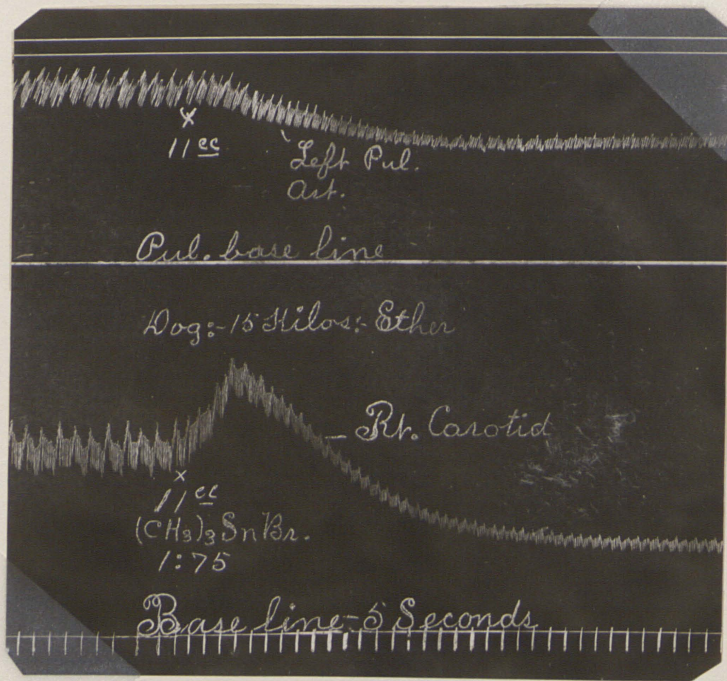


Fig. 21.

Figure 21.

PULMONARY BLOOD PRESSURE AFTER TRI METHYL TIN BROMIDE.

Figure 21 shows the action of tri methyl tin bromide on pulmonary blood pressure. The usual effect of a slight rise (due to volume injected) in systemic blood pressure followed by a prolonged fall in pressure is represented here - while there is no such marked change in the pulmonary blood pressure - just a slight lowering due probably to a weakened heart muscle. This record was made by placing a cannula in the right carotid artery and one in the left pulmonary artery - having these two canulae connected to separate manometers for recording blood pressure and having them recorded simultaneously.

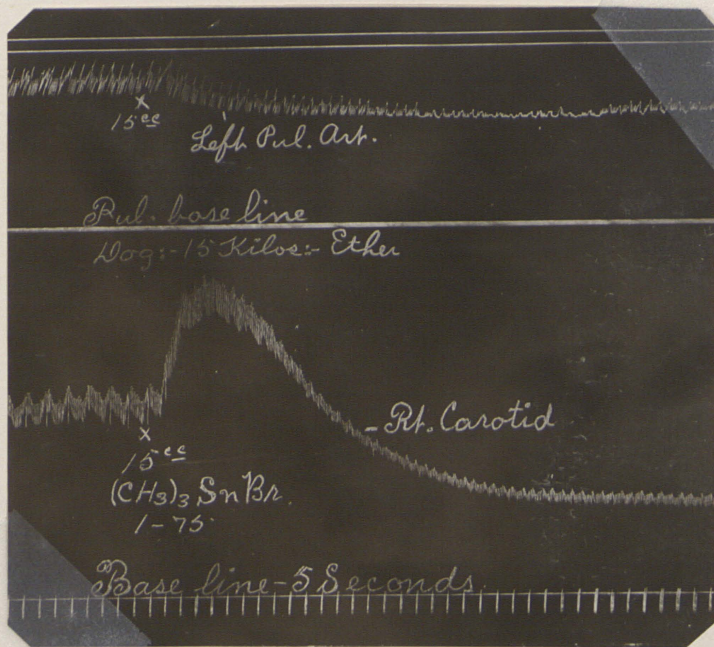


Fig. 22.

Figure 22.

PULMONARY BLOOD PRESSURE AFTER TRI METHYL TIN BROMIDE

There is shown in this figure the same phenomena as was recorded in Figure 21.

The explanation of this phenomena is given in note for Figure 21.

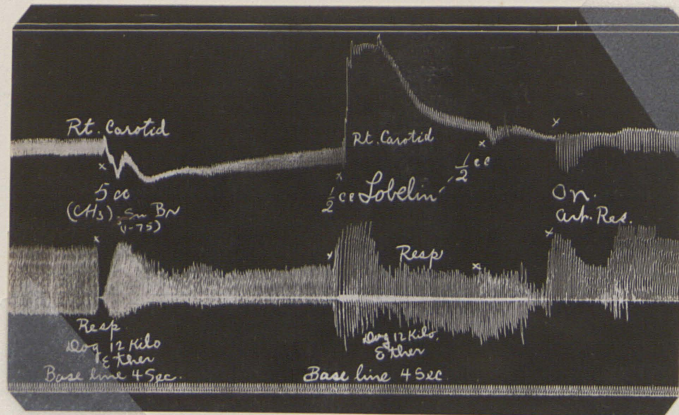


Fig. 23.

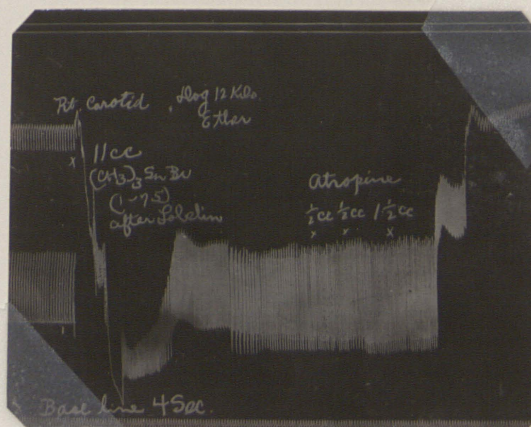


Fig. 24.

FIGURES 23 and 24.

THE USE OF LOBELIN IN EXPLAINING THE SEAT OF CARDIAC
ACTION OF TRI METHYL TIN BROMIDE.

In figure 23 there is shown on the left the typical effect of tri methyl tin bromide (i.e. before lobelin). After the animal had returned to normal a sufficient amount of lobelin was given to paralyze the ganglia (vagus) to the heart. These doses of lobelin stopped respiration so that it was necessary to resort to artificial respiration during the remainder of the experiment.

After the effect of lobelin had worn off to some extent (See Fig. 24) 11 cc. of tri methyl tin bromide (1-75 sol.) was given. Respiration was out (artificial respiration being used) so no effect was recorded here.

There was, however, a marked effect on blood pressure-- a very decided drop in pressure with the heart action resembling a vagus inhibition. It was because of this suspicious vagus effect that several small doses of atropine were given. One notes that at the point where a sufficient amount of atropine (enough to paralyze the vagus endings) was given the heart was accelerated and that the blood pressure rose. This indicates a certain amount of vagus action (peripheral endings).

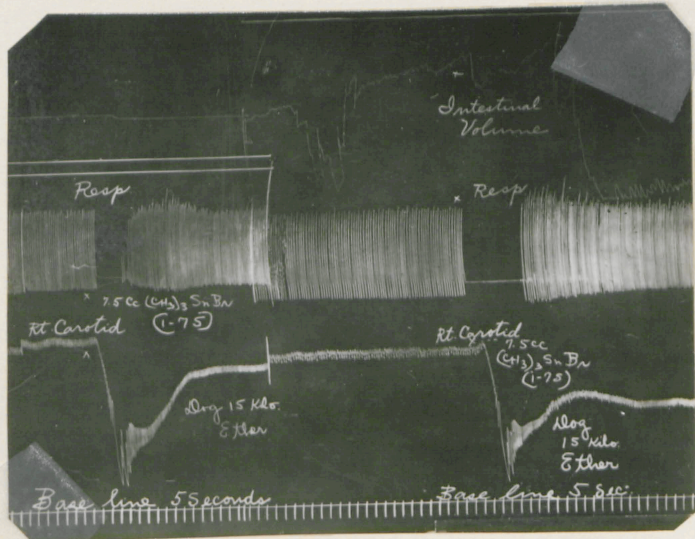


Fig. 25.

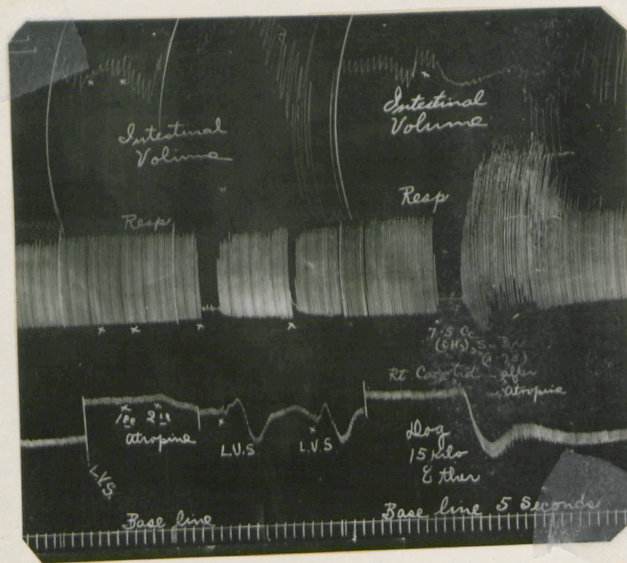


Fig. 26.

FIGURES 25 and 26.

1. THE USE OF ATROPINE IN EXPLAINING THE SEAT OF CARDIAC ACTION OF TRI METHYL TIN BROMIDE.

2. EFFECT ON INTESTINAL VOLUME.

.....

1. Cardiac Effect.

In Figure 25. we have recorded the typical effect of tri methyl tin bromide on blood pressure and respiration. One notes in the heart action a vagus-like effect and it was for this reason that we wished to study the effect of this compound after atropine had been given in sufficient amount to paralyze the vagi (cardiac) endings. This we did as is recorded in Figure 26 (left). Proof of this paralysis is shown by stimulation of the left vagus nerve with no cardiac inhibition--though there was a respiratory effect.

Thus after this amount of atropine had been given another injection (7.5 cc. 1-75 sol.) of tri methyl tin bromide was given. The effect produced on respiration by this second injection is the same as was produced by the first injection of this compound. The effect on respiration is a fall, but on the heart there is no vagus-like action, so we conclude that the vagi are paralyzed. We feel that the effect of this second injection on the heart is a depressive muscular action.

We have shown previously what we believe to be a mild peripheral vagus stimulation, and with the above we

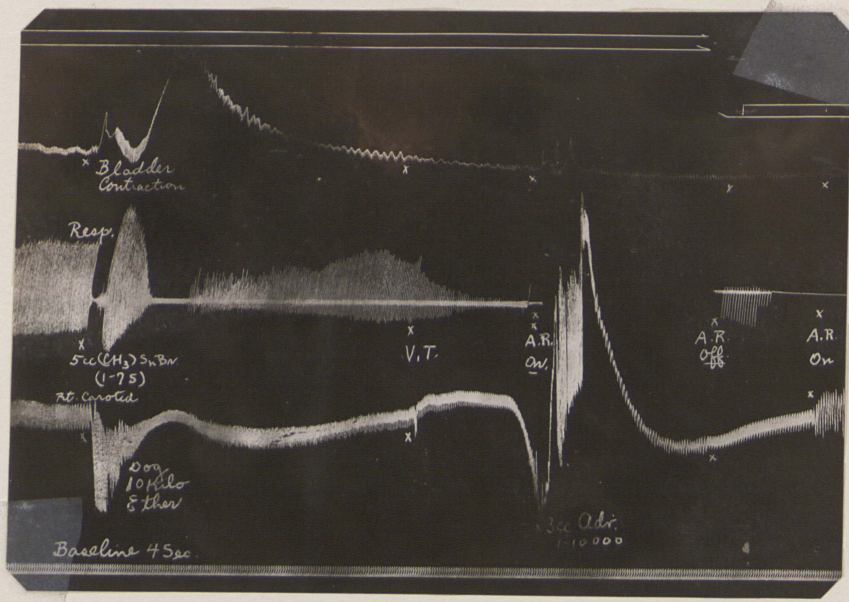


Fig. 27.

FIGURE 27.

EFFECT OF TYING THE VAGI NERVES AFTER INJECTING AN OR-
GANIC TIN COMPOUND (TRI METHYL TIN BROMIDE)

One will notice that on the first injection of this tin compound that the heart effect seems to be due to vagus action peripherally and centrally similar in many respects to the action of organic lead.

Both vagi were tied after this first injection, causing a momentary depression in blood pressure to be followed immediately by a slight rise corresponding to a break in inhibition of the vagi, which speaks for peripheral action.

Soon after the vagi were tied the blood pressure dropped to a very low level due to the latent toxicity present. Adrenalin was now injected which produced the characteristic rise in pressure, which proves the peripheral apparatus to be still active and intact. After the effect of the adrenalin wore off the animal died even though it was given artificial respiration.

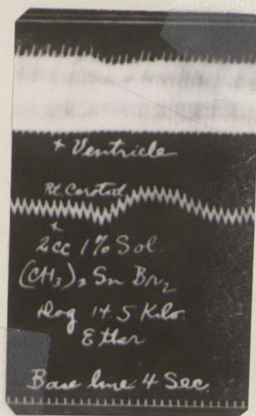


Fig. 28.

FIGURE 28.

ACTION OF DI METHYL TIN BROMIDE ON THE HEART - SMALL DOSE.

This myocardial diagram is shown to illustrate the effect of small doses of this alkyl tin bromide compound on the heart. As recorded there is a slight effect (diminution) on diastole but no change in systole. The blood pressure is raised - due to volume injected. Larger doses of this same compound produce changes in the heart comparable to those produced by like doses of diethyl tin bromide.

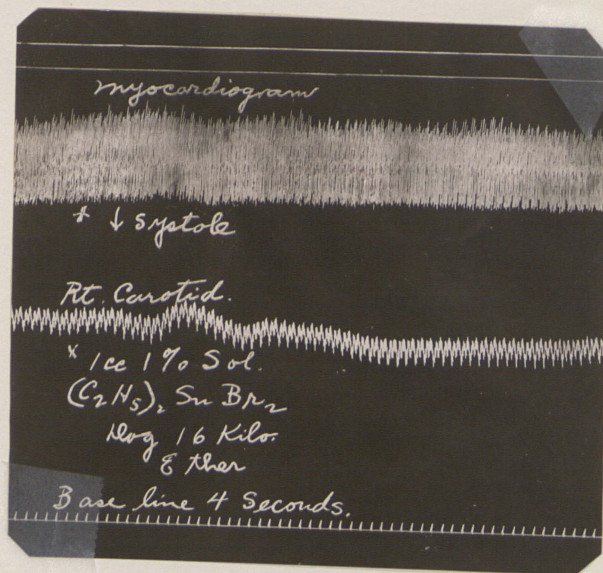


Fig. 29.

FIGURE 29.

ACTION OF DI-ETHYL TIN BROMIDE ON THE HEART - SMALL DOSE.

The effect - as shown in this myocardigram is similar to the effect produced by small doses of di methyl tin bromide. There is a slight change (diminution) in diastole but no appreciable change in systole.

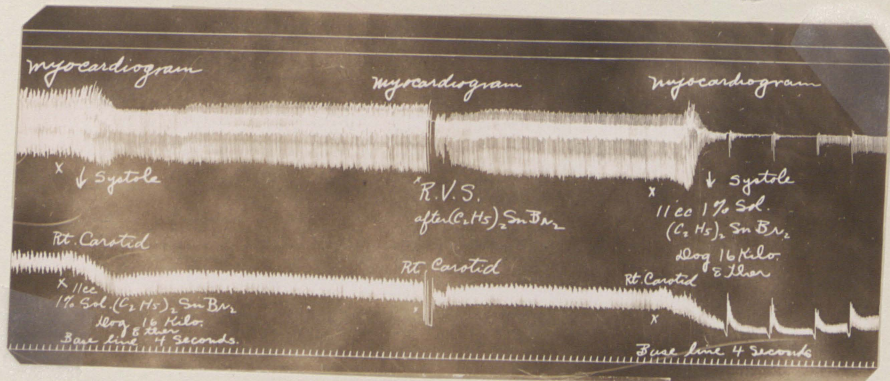


Fig. 30

FIGURE 30.

THE EFFECT OF LARGER DOSES OF DI METHYL TIN BROMIDE ON
THE HEART.

Herewith is shown the effect of a relatively large dose of this compound on the heart. There is at first a primary stimulation of both diastole and systole due probably to the temporary fall in blood pressure. This is followed by a marked diminution in both diastole and systole - due to direct muscular depression of the heart.

Followed by vagus stimulation this figure shows the vagi to be intact and when stimulated produce typical vagus action.

A second dose (same amount) of the compound is now injected. The effect is the same as was produced by the initial injection but much more marked. Convulsive movements also took place as shown in temporary changes (rise and fall) in blood pressure. This is recorded near the end of the figure.

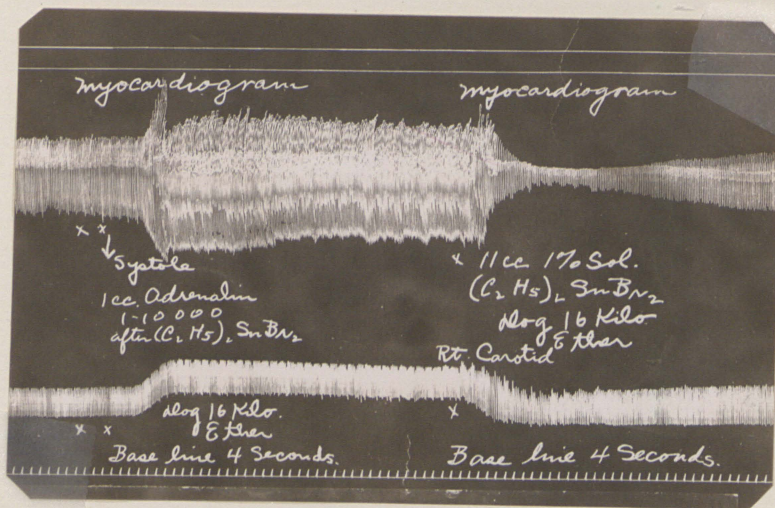


Fig. 31.

FIGURE 31.

FURTHER ACTION OF DI ETHYL TIN BROMIDE ON THE HEART AFTER
ADRENALIN.

This figure is a continuation (same experiment) of Figure 30. The dog became very weak (blood pressure low, etc.) and it was for this reason that adrenalin was injected. The typical action of adrenalin is here recorded.

The injection of adrenalin is followed by an injection of di ethyl tin bromide. The effect produced is similar in nature and extent as was produced by previous injections of this compound shown in Figure 30.

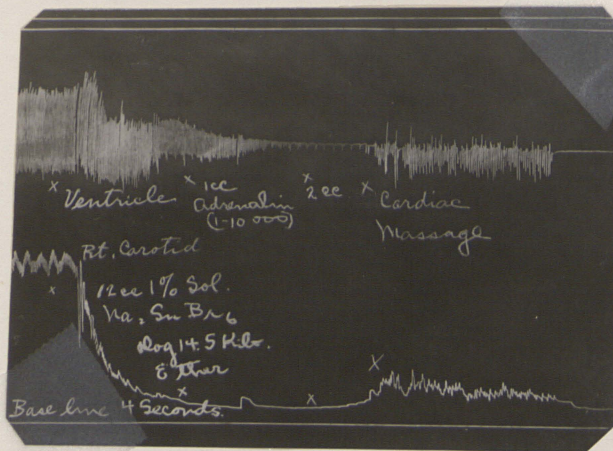


Fig. 32.

FIGURE 32.

ACTION OF SODIUM TIN BROMIDE ON THE HEART - LARGE DOSES.

This tin compound seems very toxic for laboratory animals. We feel reasonably sure that its effect is not due to emboli (coronary) as we tested 1% solution of this compound with blood in a test tube previous to injection and noted no change.

We see, however, in this experiment that the action on the heart is very pronounced. There is a marked diminution in systole and diastole to complete stoppage of the heart. Heart massage and adrenalin failed to revive the animal.

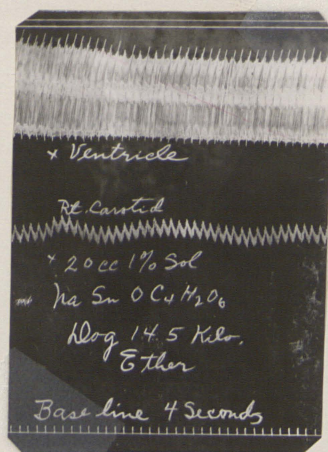


Fig. 33.

FIGURE 33.

ACTION OF SODIUM TIN TARTRATE ON THE HEART.

This figure shows that the compound sodium tin tartrate has no effect on the heart or blood pressure. The effect on the heart was recorded by means of a myocardiograph. This observation is in keeping with data submitted later, this data showing sodium tin tartrate to be inert as far as heart action and respiration are concerned.

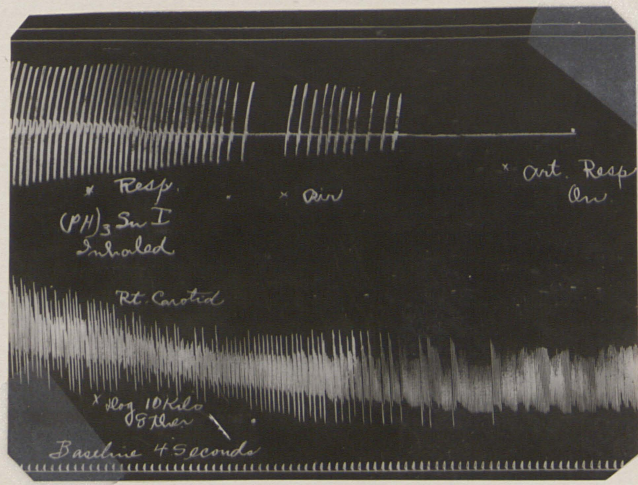


Fig. 34.

FIGURE 34.

ACTION OF INHALED TRI PHENYL TIN IODIDE ON RESPIRATION AND
BLOOD PRESSURE.

Method of Administration.

. About 1 gram of this salt is placed in a test tube - the test tube being connected by means of a rubber hose to a tracheal cannula (2 way one-- for ether and for air). The ether is discontinued after which a flame is placed under the test tube containing the volatile tin compound. By this method the fumes of tri phenyl tin bromide are taken into the respiratory tract and the effect on respiration and blood pressure recorded.

As shown respiration is diminished in rate and volume. Blood pressure is lowered at the same time. It was necessary later to resort to artificial respiration, even though the fumes had been removed some time before.

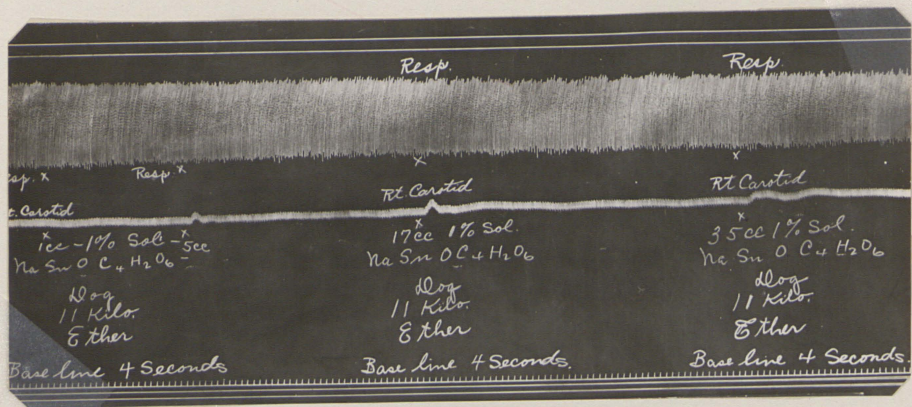


Fig. 35.

FIGURE 35.

ACTION OF SODIUM TIN TARTRATE ON BLOOD PRESSURE AND RESPIRATION.

A large dose of this compound (35 cc.) was injected intravenously. As shown there was no change in respiration and no change in blood pressure except a slight temporary elevation (due to large volume injected) which returned to normal quickly. In all cases where this compound was given the same phenomenon occurred. This in marked contrast to the effect of the alkyl organic tin compounds on blood pressure and respiration.

This tracing shows the action of graded doses as well as the larger dose of 35 cc. 1% solution.

We conclude in this case that Sodium Tin Tartrate is a relatively inactive compound.

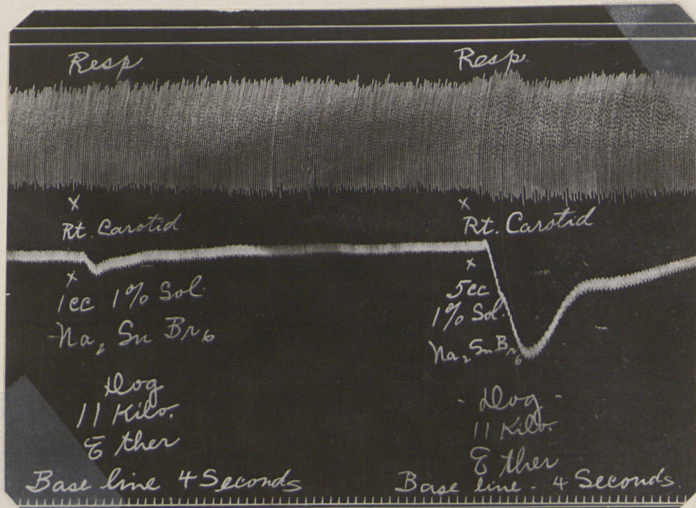


Fig. 36.

FIGURE 36.

EFFECT OF SODIUM TIN BROMIDE IN SMALL DOSES ON BLOOD PRESSURE AND RESPIRATION.

Small doses of sodium tin bromide produce little or no change in either blood pressure or respiration. Large doses produce similar changes in blood pressure and respiration as did like doses of the alkyl tin bromide compounds - but milder in nature. The effect on respiration, however, is much less marked than with the alkyl tin bromide compounds. It is difficult to estimate how much of the respiratory stimulation is due from the asphyxia caused by the sudden drop in blood pressure.

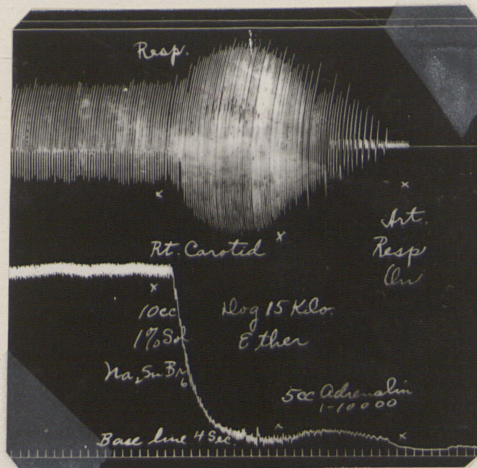


Fig. 37

FIGURE 37.

EFFECT OF SODIUM TIN BROMIDE IN LARGE DOSE ON EXPERIMENTAL
ANIMAL.

As shown in this tracing the effect of a very large dose of sodium tin bromide is very similar to the effect produced by a like dose of the true alkyl tin bromide compounds.

In this experiment the effect on respiration was the primary depressive, secondary stimulation followed by the usual tertiary depression- in this case total suppression and death.

The effect on blood pressure was no primary elevation (due to volume injected) followed by a marked fall in pressure to zero. As stated before asphyxia plays an important role here.

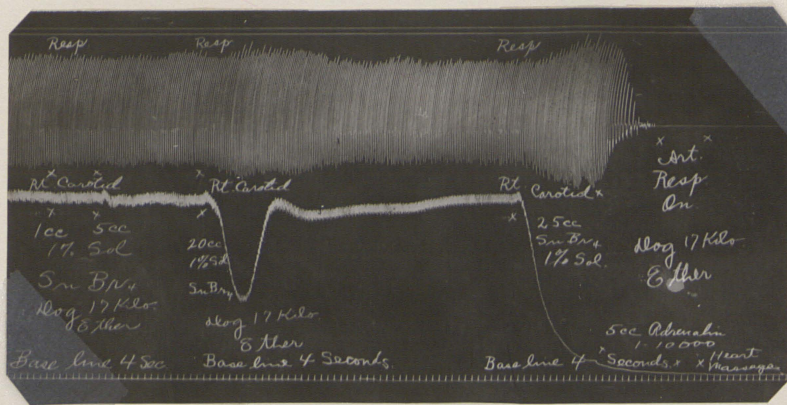


Fig. 38.

FIGURE 38.

ACTION OF TIN (STANNIC) BROMIDE ON BLOOD PRESSURE AND
RESPIRATION.

We have shown here the effect of four, graded doses of tin bromide on respiration and blood pressure. As shown, small doses have no effect on either respiration or blood pressure while larger doses affect both. Respiration is slightly stimulated and later depressed, to respiratory failure often, while blood pressure shows a marked fall to zero if stimulants are not given. We feel that some of the increase in respiratory movements may be due to the fall in blood pressure, i.e., due to the asphyxia which is produced. As a comparison of this salt with sodium tin bromide and sodium bromide we feel that it (Sn Br_4) is less active than $\text{Na}_2\text{Sn Br}_6$ but much more active than NaBr .

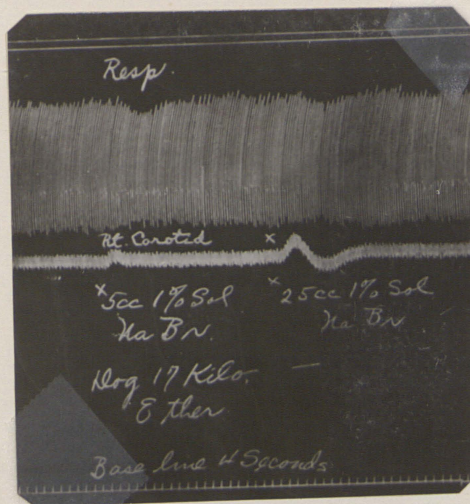



Fig. 39.

ACTION OF SODIUM BROMIDE ON BLOOD PRESSURE AND RESPIRATION.

We include this figure as a comparison using the same sized doses between sodium bromide and tin (stannic) bromide.

Comparing the results obtained here with those obtained in Figure 38 one can see clearly that the tin bromide has a much more depressant effect than has sodium bromide. For this reason we feel that the activity is due mainly to the tin (stannic) radical rather than to the bromide radical.



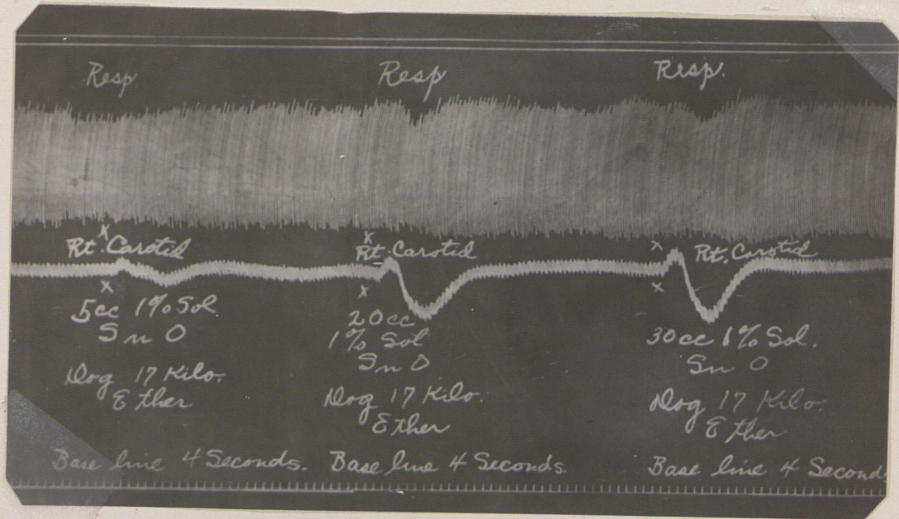


Fig. 40.

FIGURE 40.

ACTION OF TIN (STANNIC) OXIDE ON BLOOD PRESSURE AND RES-
PIRATION.

We submit these tracings to show the action of tin combined with a relatively harmless radical (Oxide). In this way we are able to compare the activity of Tin Bromide with the Tin Oxide. In very large doses (30 cc. 1% sol.) there is much less activity shown than when equal amounts of the alkyl tin compounds are injected.

I. Absorption:

Soluble Organic Tin Compounds are absorbed by the gastric-intestinal tract, subcutaneously, intramuscularly or intravenously. Proof of their absorption lies in the following facts that (1) they produce toxic signs and symptoms and (2) that tin is found in the urine 36 to 72 hours after administration - time of detection depending on route given.

The above data follows very closely the facts concerning the absorption of lead. Both tin and lead have been reported by other workers as capable of being absorbed thru the skin. We have done no work concerning the absorption of organic tin compounds via this route.

Insoluble Inorganic Tin Compounds are absorbed after intraperitoneal injection. Proof of their absorption is (1) Toxic symptoms produced (2) Detection of tin in the urine and (3) in one instance the odor of one compound (tri ethyl tin hydroxide) could be detected on the animal's breath.

We feel reasonably sure that these compounds could be absorbed via respiratory system. Other routes offer no advantages for absorption as these compounds are very insoluble in all the ordinary solvents.

II. Poisoning:

Soluble Organic Tin compounds are capable of producing signs and symptoms of acute tin poisoning when given in sufficient doses by mouth. These compounds are capable of producing the same (though less severe and more chronic) symptoms when given subcutaneously or intramuscularly. When given intravenously poisoning and death occur quickly - the lethal dose varying with the individual (experimental) animal.

Insoluble Organic compounds do not produce signs of tin poisoning by mouth. They do, however, when given intraperitoneally and produce death in small doses (700 to 800 milligrams).

We feel that, in excessive amounts, the respiratory tract offers a route of absorption and from our data it seems evident that poisoning does occur after such absorption.

III. Relative Toxicity of Compounds.

The activity of the soluble organic tin compounds and the insoluble compounds as well, is in direct proportion to the relative amount of tin present in the molecule. We conclude from this observation that these organic compounds owe their activity in a major degree to the tin atom present.

IV. Latent Toxicity.

In some cases (relatively few) after an initial injection of an organic compound the animal revives for some minutes and allowing the dog to have plenty of air and restoratives (stimulants) we are not able to save the animal's life. We explain this effect as being one of latent toxicity.

V. Idiosyncrasy.

Many drugs show an idiosyncrasy to some individuals and in some cases. In the case of the organic tin compounds we have found that it requires a very small dose to kill some animals or to render them inactive thereafter. We explain this action as being one of special (or individual) idiosyncrasy.

VI. Pathology.

(A) Externally (Mucous Membranes)

We have shown that the fumes of the insoluble organic compounds are very irritating to the nasal mucous membrane of the experimenter (man) and to the respiratory mucous membrane of the experimental animal (dog). The reaction produced in each case is one of simple inflammation.

(B) Locally (At Site of Injection)

The soluble organic compounds produce at the site of injection (i.e. either subcutaneously or intramuscularly) a marked reaction--inflammatory in nature. This reaction persists for about ten days after which time it subsides without leaving any signs of necrosis.

(C) General (Systemic Effect.)

Whether these compounds are given by mouth intravenously, intraperitoneally (insoluble ones), intramuscularly or subcutaneously a systemic toxic effect is noted. This takes the nature of a systemic poisoning or toxemia. All organs are affected, the heart, liver and kidneys showing the greatest damage. The reaction (general) produced is typical for systemic poisons.

(D) Specific (Organs and Tissues).

(See notes of pathological changes produced under specific organs and tissues.)

VII. Action on Heart.

We have shown two different and independent heart effects viz: (1) a peripheral vagus stimulation which slows the heart and a (2) direct depressive effect on the heart muscle. These two phenomena are variable as either may act alone (independent of the other) or in conjunction with the other. A third (3) phenomenon may be present viz. a central vagus stimulation as the vagus center is near the respiratory center and vaso-motor center and we have felt that there may be some central vagus stimulation. It will require some further experimental work to prove this point however.

Myocardiograms show clearly the depressant action on the heart muscle as shown in changes in the ventricle.

VIII. Effect on Respiration.

We may summarize the effect on respiration in three phases, viz.

(1) No effect after small doses.

(2) Central action (Respiratory Center) in larger doses- as

(A) Primary stimulation

(B) Secondary Depression.

(3) Very Large Doses.

(A) Stoppage of Respiration due to marked depression (suppression) of the respiratory center or over stimulation of this center leading to stoppage.

(B) Stimulation of respiration either central stimulation, asphyxial or both.

(C) Tertiary depression of center some times to stoppage, but never to a previous return of normal respiration.

IX. Systemic Blood Pressure.

All the soluble organic tin compounds produce a primary rise in pressure (due to volume injected) followed by a marked fall (due to a weakened heart muscle and to vagus stimulation). The blood pressure returns to normal after some minutes due in part to some vaso-constriction (stimulation of vaso-motor center). Insoluble inorganic tin compounds when inhaled produce a slight lowering of pressure.

X. Pulmonary Blood Pressure.

There is produced when soluble organic tin compounds are given intravenously a slight lowering of pulmonary pressure due we feel to a weakened heart muscle.

XI. Splenic Volume.

There is a marked diminution (contraction) in splenic volume. We explain this phenomenon on the basis of vaso-constriction or vaso-motor stimulation in the medulla. This causes a rise in blood pressure as the spleen (and other organs) contract.

XII. Kidney Volume.

The same principle is involved here as in case of splenic volume. Our records show a diminution in kidney volume also.

XIII. Bladder Contractions.

Soluble organic tin compounds produce contractions of the bladder which are secondary to the asphyxia. (produced by lowered blood pressure).

XIV. Intestinal Volume.

We found no appreciable change in intestinal volume after intravenous injections of soluble organic tin compounds.

XV. Liver Volume.

There is a slight diminution in liver volume (due to vaso-constriction) when soluble organic tin compounds are given intravenously.

XVI. Lung Volume.

The one soluble organic tin compound tri methyl tin bromide failed to produce any appreciable change in lung volume. After several injections, however, there seemed to be a very slight diminution in lung volume. This finding is in direct contrast to most other heavy metals as some dilatation (increase in volume) is generally produced.

XVII. Stomach Contractions.

Soluble organic tin compounds do not produce any change in stomach contractions after these contractions are aroused by previous injections of barium.

XVIII. Effect of Inhaled Insoluble Compounds.

(1) Man (Nasal Mucous Membrane)

The fumes of the insoluble compounds when inhaled give one an intense irritation and a severe headache which lasts for several hours.

(2) Dog's Bronchial Mucous Membrane.

When the fumes of the insoluble organic tin compounds are given to a dog intratracheally there is a marked depression of respiration (in rate and depth of breathing). The blood pressure falls and the heart action becomes weaker. Death would occur, we believe, if the fumes were not removed.

XIX. Excretion.

Soluble Organic Tin Compounds when given intravenously, subcutaneously intramuscularly or by mouth are excreted in the urine.

Insoluble Organic Tin Compounds when given intraperitoneally are excreted by the lungs (evidence is odor on breath), in the urine and in the gastric contents.

We feel reasonably certain that tin (like lead) is excreted in various other secretions. In order to prove this point, however, additional experiments must be performed.

XX. Death.

The cause of death from both the organic and inorganic tin compounds is a respiratory failure (depression and paralysis of the respiratory center) as respiration ceases long before the heart action.

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