THESIS.

PART ONE.

EVIDENCE OF SYSTEMIC INTERACTION OF IODINE AND SODIUM THIOSULPHATE.

by

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EVIDENCE OF SYSTEMIC INTERACTION OF IODINE AND SODIUM THIOSULPHATE.

Iodine first came into general use as a disinfectant of wounds and in the preparation of the skin of the operative field, about fifteen years ago. It was used previously in surgery for securing adhesive inflammation of serous cavities and cysts. It produces a mild but deep and persistent irritation and if repeatedly applied leads to vesication and necrosis of the skin or tissue. The clinical use of iodine as an antiseptic hasbeen very successful, even dirty infected wounds healing rapidly.

The widespread use of iodine by the medical profession has popularized its use by the laity. At the present time it is a common household remedy. The most common preparation is the official tincture of the United States Pharmacopoeia, containing seven per cent iodine and five per cent potassium iodide, sold under the poison label.

Cases of poisoning from iodine are reported more frequently as its use increases, partly accidently, in the course of its therapeutic use, or from suicidal intent.

IODINE POISONING.

Poisoning with iodine can be divided into two groups. One group constitutes those cases of comparatively mild poisoning occurring with large therapeutic doses and described by the term

"iodism". These symptoms of mild poisoning are exhibited after comparatively small therapeutic doses in those manifesting an idiosyncrasy towards the drug. These cases of iodism require simply withdrawal of the drug and elimination of that remaining.

Serious poisoning with iodine usually occurs in those taking the drug with suicidal intent, or those taking it by accident. The fatal dose is one fluid dram of the tincture. This is a seven per cent solution in alcohol so that the amount of iodine present in the average fatal dose amounts to 0.28 grams corresponding to 4 1/5 grains. One feature of importance in the routine symptomatic progress of iodine poisoning is the continually increasing depression, evidentally of the central nervous system, leading to coma and death in from twenty-four to thirty hours. The latter time seems to be the more common duration of the fatal cases.

In studying the treatment of iodine poisoning, a knowledge of the action of this element becomes of fundamental importance. Though iodine and iodides are among the most commonly used of drugs, we know but little of their manner of action. Professor Sollman[1] make the following conclusions in a study entitled, "The Fate of Iodine, Iodides and Iodates in the Body"(1).

v. "----neither iodide nor iodate undergo any change in the serum. Free iodine is promptly bound, with the formation of iodide but no iodate is formed, even in the presence of alkali, so that subsequent acidulation does not liberate iodine ------"

vi. "Large doses of free iodine, administered by stomach, exist in the blood solely as iodide. The addition of acid to the blood does not regenerate iodine."

"The alkalinity of the body is not sufficient to bind any noticeable quantity of free iodine- even in the absence of proteins and aromatic groups."

1. "The blood after the administration of free iodine does not liberate iodine on acidulation, because the iodine is bound through the protein and not through the alkali."

2. "Free iodine cannot be liberated in the body, since all the conceivable reactions for the liberation of iodine from its compounds require much higher hydrogen-ion concentrations than exist anywhere in the body."

The protein-iodide combination responsible for the toxic effects of iodine, must be the same as that existing in the superficial tissues when iodine is applied locally. The stain produced by iodine upon tissue is removed rather quickly and permanently by immersing the part in a solution of sodium thiosulphate. The local irritation is stopped at the same time. This chemical reaction occuring in the superficial tissues suggests the possibility of producing the same reaction in the systemic circulation and all the tissue supplied by the blood.

In reviewing the literature on iodine only two references are found pertaining to the interaction of iodine and thiosulphate in living tissue. One of these is an article entitled, "IL jodio come antisettico e l'iposolfito di sodio come antidoto al jodio", reporting work of Sabbatani's[2] on the counteraction of iodine

held on the skin, by sodium thiosulphate. Snoy[3] also employed this reaction for the purpose of removing iodine stains. Sabbatani believes the reaction to be between two molecules of sodium thiosulphate and one of iodine resulting in a compound ro which he assigns the formula ($Na_2S_4O_6$).

The symptoms produced by iodine in toxic amounts are described as follows in Holland's[4] toxicology: "It acts as a powerful irritant upon the stomach and bowels, causing pain in the mouth, throat and stomach, vomiting and purging, extreme thirst, fainting attacks and collapse. When applied by surgeons freely to absorbing surfaces, it ma cause systemic disturbances, such as headache, dizziness, mental trouble, along with the above gastric symptoms brought on inderectly. Its elimination by the kidneys involves those organs in inflammation, which may end in suppression of urine."

The treatment of iodine poisoning can best be described by quoting from texts on the subject of toxicology. Some of the texts make no suggestion aside from the attempt to combat the symptoms as they arise. Dwight and Peterson[5] state: "Emesis and catharsis are indicated. There is no definite chemical antidote, but, on account of the affinity of iodine for starch, farinaceous foods and liquids have a favorable action."

Brundage[6] states under treatment of iodine poisoning: " Evacuate the stomach: syphon out the stomach with a stomach tube: using plenty of water. If a stomach tube is not at hand, use an

emetic, such as zinc sulphate (20 grains in two tablespoonsful of water, repeated in ten to fifteen minutes if vomiting is not produced), or mustard (a tablespoonful in a small cupful of water, repeated in fifteen minutes if not effective), or ipecacuanha (powdered ipecacuanha 30 grains or syrup of ipecac a teaspoonful, every ten to fifteen until vomiting results), or apomorphine hydrochloride, hypodermically ($^{1}/_{10}$ grain repeated every fifteen minutes until effective). After giving the emetic give plenty of lukewarm water to encourage vomiting. Starch is the best antidote for free iodine, forming iodide of starch. Promptly and freely give large quantities of starch, wheat flour or arrowroot water (water made by boiling starch in water or by pouring boiling water upon such), or give sodium thiosulphate (20 grains in two tablespoonful of water). The stomach must be evacuated soon after giving the antidote, as the compound is not altogether inactive. Also give sodium bicarbonate." The treatment is further continued, advising the use of whiskey, aromatic ammonia, strychnine, atropine, digitalis, caffeine, amyl nitrite, and strong coffee. Artificial heat and opium are further advised.

Holland[7] outlines the treatment for iodine poisoning as follows: "Large drafts of warm water will assist in evacuating the stomach. The antidote is starch in some form, best given in decoction, such as the clear starch of the laundry; or as gruels, boiled rice or arrowroot, given as long as the vomited matter has a blue color."

It is of interest to note the variety of remedies and methods of treatment advised in the different texts on toxicology for iodine poisoning. They indicate a lack of any specific antidote. None of them offer any means of counteracting the drug once it has passed into the physiological interior of the body. Iodine is volatile and rapidly absorbed. Death usually occurs after twenty-four to thirty hours, from the action of the absorbed iodine. The remedies advocated by the toxicologies uniformly aim to counteract local irritation of the alimentary mucosa and unabsorbed iodine. Their field as antidote is therefore limited in application and in utility.

It has long been known that sodium thiosulphate will combine with free iodine ($2Na_2S_2O_3 2I = 2NaI\ Na_2S_4O_6$). This reaction has been made use of by Snoy[3] for the purpose of removing iodine stains. Experiments by Sabbatani[2] demonstrated that sodium thiosulphate could be used locally to counteract the action of iodine on the skin. There is no report in the literature, however, of its being tried to counteract iodine when in the systemic circulation.

The following work was undertaken to determine whether the interaction of iodine and sodium thiosulphate occurring in the superficial tissue would occur generally throughout the body from the systemic circulation; with a view to its employment as a specific antidote in iodine poisoning.

It was necessary for the success of our ezperiments that the resulting iodine compound be much less toxic than the free iodine.

The National Formulary standardizes a Tinctura Iodi Decolorata which is a hydro-alcoholic solution of iodine to which sodium thiosulphate is added to render the solution colorless.

To determine the toxicity of the iodine compound we chose this colorless tincture.

It was first necessary to establish a minimum lethal dose of each substance for the rabbits we were to use. Sollman[8] quotes figures given by other investigators, giving 0.075 grams of the element iodine per kilo of rabbit and 1.5 to 2.0 grams per kilo of sodium thiosulphate as a minimum lethal dose of each given hypodermically.

DETERMINATION OF TOXICITY OF IODINE DECOLORATA.

The toxicity of the decolorized tincture of iodine, which contains by weight 83.0 milligrams of iodine and 83.0 milligrams of sodium thiosulphate per cubic-centimeter, was determined. One cubic-centimeter of decolorized tincture of iodine, (equalling 166.0 milligrams), per kilo of rabbit was injected hypodermically. No sign of any reaction could be detected. It was concluded that the decolorized tincture of iodine was for all practical purposes non-toxic.

Confirmation of Sollman's figures for the establishment of a minimum lethal dose of iodine and sodium thiosulphate was next begun.

DETERMINATION OF M. L. D. OF IODINE.

The first rabbit was given 83.0 milligrams of iodine per kilo in the form of the official tincture. No symptoms of toxicity developed. This tincture was diluted 1:3 with distilled water and injected subcutaneously in different areas so as not to cause too great tissue

destruction in any one place. These dosages were gradually increased on different animals to 150.0 milligrams per kilo of the element iodine before any toxic symptoms appeared. There were signs of depression lasting for about twenty-four hours. The urine contained no blood, no albumen, no free iodine. The dosage was gradually increased to 190.0 milligrams per kilo. This dosage caused marked dyspnea, followed by central depression within thirty minutes after the injection. The respirations became shallow and slow. The animal became very weak, developed a slight tremor, it had difficulty in regaining its feet when rolled on its side; the central depression deepened and collapse developed; the respirations were irregular and shallow; ninety-six hours after the injection the rabbit died of respiratory failure.

The urine was reddish-brown, contained blood, and a large amount of combined iodine, i.e. it colored starch blue only after treating treating with acid. The post-mortem revealed no very marked changes. There was no fluid in the peritoneal or pleural cavities, or edema of the lungs. The kidneys appeared engorged and hyperemic, dark purple in color. Histological examination revealed an intense hyperemia with extravasation of blood into the uriniferous tubules and between the glomerular tufts and Bowman's capsules. The renal epithelium did not appear damaged.

The minimum lethal dose for these animals evidently lay around 180.0 to 190.0 milligrams per kilo as the element iodine given in the form of the tincture. All subsequent experiments in which the rabbits received over 190.0 milligrams per kilo died. One rabbit which received 210.0 milligrams died after eleven hours with symptoms above described. But no animal receiving under 180.0 milligrams per kilo was lost.

It will be noted that these figures are considerably higher than those quoted by Professor Sollman. The rabbits we used had been reared entirely out of doors. They were very vigorous adult animals with high resistance. We attributed the higher figures their splendid physical condition.

DETERMINATION OF COMPARATIVE TOXICITY OF SODIUM THIOSULPHATE.

The sodium thiosulphate was given in the form of a ten per cent aqueous solution subcutaneously. The dosage was gradually increased with each succeeding animal, watching carefully for any toxic manifestations. Three grams per kilo were given the last rabbit. No toxic symptoms were observed. A volume of thirty cubic-centimeters was necessary for this dose. A hypodermic of this volume caused considerable tissue damage. We feared that the results of trauma from larger doses would confuse any toxic manifestations.. Also, the high dosages we had safely given, convinced us that the drug was comparatively non-toxic, and that it could be ruled out of our calculations so far as its toxicity was concerned.

EVIDENCES OF SYSTEMIC INTERACTION OF IODINE AND SODIUM THIOSULPHATE.

We next worked to counteract the toxic action of iodine by sodium thiosulphate. The first rabbit was given one gram per kilo of sodium thiosulphate in the form of the ten per cent aqueous solution, and 250.0 milligrams of iodine per kilo in the form of the official tincture; each injected subcutaneously, the iodine after the sodium thiosulphate, in areas removed from each other that there might be no local irritation between them. The iodine solution was diluted 1:3 with distilled water and injected in several different places to avoid tissue destruction. This animal developed no toxic symptoms and ate well. The urine was clear, neutral in reaction, contained a small amount of albumin, considerable amount of combined iodine, no free iodine. At the end of five days all traces of iodine and albumin had disappeared from from the urine.

The next dosage was 300.0 milligrams per kilo of iodine and one gram of sodium thiosulphate. The results were similar to those of the first experiment, except there were signs of gastro-intestinal irritation an hour after injection.

In the succeeding experiment, 310.0 milligrams of iodine per kilo and one gram of sodium thiosulphate were administered. The animal manifested some desire to eat, but after five hours developed some pain referable to the abdomen. It received 0.2 gram injections of sodium thiosulphate at two hour intervals the first day, given subcutaneously. At the end of the seventh day the urine was free of iodine and albumin, and the animal appeared perfectly normal.

The next rabbit received first, 0.5 gram of sodium thiosulphate in the form of a ten per cent solution followed immediately by 320.0 milligrams of iodine per kilo, both subcutaneously; 0.3 gram of sodium thiosulphate (ten per cent aqueous solution) was then given intravenously. Within two hours the animal was in a state of collapse, it lay prone and limp, there was marked hyperpnea, the respirations were shallow, the heart rapid and weak. The 0.3 gram dose intravenously was repeated. Within fifteen to twenty minutes after the administration of the sodium thiosulphate the animal regained its feet and thereafter moved about in its cage occasionally. The intravenous injection was repeated in three hours.

The urine was murky-brown in color and thick, neutral in reaction, it contained some albumin, and considerable amount of combined iodine. In five days this animal's urine was clear of iodine and albumin, and it had apparently recovered.

The injection of the salt directly into the blood stream was given with the hope that a more rapid reaction would be possible. We were encouraged by the results of this experiment. We concluded that small amounts of the salt, given at frequent intervals, subcutaneously and directly into the blood stream offered the best way of counteracting the iodine.

The next animal received 340.0 milligrams of iodine per kilo, one intravenous injection of 0.2 gram sodium thiosulphate immediately following, and 0.2 gram doses of the salt subcutaneously at hour intervals thereafter for the next twenty-four hours. This animal recovered nicely without showing any very toxic symptoms beyond a hemorrhagic nephritis which developed within twenty to thirty minutes

after the iodine injection.

In the next seven experiments, doses from 350.0 to 375.0 milligrams of iodine per kilo were given. The sodium thiosulphate was given every hour subcutaneously for twelve hours and every hour intravenously for twenty-four hours, in 0.2 gram gram doses. All of these animals died within twenty-four hours from respiratory paralysis. Symptoms of deep central nervous depression and severe gastro- intestinal distress were noted.

As the above symptoms with which these animals died corresponded rather closely with those which occur when toxic doses of sodium thiosulphate are injected intravenously, as stated by Professor Sollman[9], -central depression, and cardio-vascular collapse,- we suspected that our antidote might be a factor in the cause of death when administered in this manner. To ascertain whether or not the intravenous method was a wrong one, the next animal was not given any intravenous injections of sodium thiosulphate but received hourly injections of 0.2 gram subcutaneously, following a dosage of 360.0 milligrams of iodine per kilo. This animal died after forty-eight hours. It did not exhibit so great a central depression as those rabbits which had received the intravenous treatment. The gastro-intestinal distress, however, was marked, large quantities of combined iodine were present in the urine, and considerable amounts of sodium thiosulphate. This was tested for in all the rabbits' urines by observing how many drops of urine were required to decolorize one drop of the official tincture of iodine. We endeavored to maintain such a concentration of sodium thiosulphate in the system, so that four to five drops of the urine would completely decolorize one drop of the tincture.

Post-mortem examination of the above rabbit revealed a stomach filled with food and intensely contracted throughout. The food material was very dry, the mucosa of the stomach came away when the food was removed, the whole mucosa of the stomach appeared necrotic. There was no fluid in the peritoneal or pleural cavities, the lungs were normal in appearance, the kidneys and spleen, dark purple in color, liver, normal in color.

With the idea that the gastric irritation was coming from the iodine excreted into the stomach, the next rabbit was given the same dosage, (360.0 milligrams of iodine per kilo), but received one-tenth to one gram doses of sodium thiosulphate per stomach tube, in addition to the subcutaneous hourly injections of the same. After one hours time this animal was quite depressed, but the symptoms did not increase. He gave evidences of abdominal pain. Blood was present in the urine for eight hours after the injection of the iodine. The administration of the salt per stomach tube seemed to cause some distress and active peristalsis was exhibited afterward. Semisolid stools followed. The animal showed a desire to eat after forty-eight hours. The urine was free from iodine and albumin on the fourth day after the injection of the iodine.

By following this method of procedure, i.e. frequent subcutaneous injections of sodium thiosulphate; administration of one gram of the same per stomach tube, we were able in the next four experiments to increase the iodine dosage from from 360.0 milligrams per kilo, to

450.0 milligrams per kilo without any more severe symptoms than the 340.0 milligram dose caused. We had one fatality with an animal which had recovered from a 375.0 milligram dose, apparently from a septicemia due to infection at one of the injection points.

The animals receiving 450.0 milligrams of iodine per kilo recovered rapidly without any marked effects. In giving so large a dose as 450.0 milligrams of iodine per kilo as the element iodine in the official tincture, 15.5 cubic-centimeters of solution was necessary. It was impractical to dilute to more than thirty cubic-centimeters, on account of limitation of subcutaneous area. This factor prevented us from going higher with our dosage.

This last animal was killed by chloroform six months later. Post-mortem examination revealed no abnormalities beyond the cicatrixes at the iodine injection points.

CONCLUSIONS.

We had counteracted over two and a half times the minimum lethal dose of iodine with sodium thiosulphate.

It seems logical to conclude that sodium thiosulphate will combine with iodine in the systemic circulation and tissues to form a comparatively non-toxic compound.

Sodium thiosulphate is sufficiently non-toxic to the rabbit in doses necessary for the treatment of iodine poisoning, when given hypodermically or by stomach tube.

It should be noted also, that 3.8 per cent of the official tincture of iodine is iodine in the form of iodide. The rabbit receiving 450.0 milligrams of iodine per kilo as the element, received also 182.13 milligrams of iodine in the form of iodide, totalling 632.13 milligrams of iodine received per kilo. The toxicity of the iodide as reported by Boehm[10] undoubtedly added to the toxicity of the doses as given.

A relative dose of the last for a seventy kilogram man would equal 44.249 grams.

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THESIS.

PART TWO.

THE EFFECT OF SALICYLATE ADMINISTRATION ON THE ACETONE BODY CONTENT OF THE BLOOD.

by

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THE EFFECT OF SALICYLATE ADMINISTRATION ON THE ACETONE BODY CONTENT OF THE BLOOD.

Langemede reporting in the Lancet[1], calls attention to the acidosis occurring in children under salicylate treatment. These children were ill in hospitals suffering from acute rheumatic fever. Constipation was a constant symptom according to the report.

McNerty reports a case of poisoning in the Northwest Medicine[2] of a three year old boy who drank three drams of methylsalicylate. He had been in apparently normal health. McNerty mentions dyspnea, and rapid pulse among the symptoms which developed before death.

Myers in the Jr. A.M.A.[3], reports a case of methyl-salicylate poisoning in a boy of two years. The symptoms came on after twenty-four hours. The most pronounced of these were cinchonism, vomiting, and dyspnea. Acetonuria was present to a degree similar to that seen in diabetic coma. the extreme air hunger (Kussmal breathing), and high acetone body content of the urine were the most marked features of this case. The case did not end fatally, however.

The salicylates are among the most widely and freely used of drugs. It becomes pertinent after studying the above reports to know whether or not the salicylates play any role in the production of acidosis and acetone bodies. No mention is made elsewhere in the literature of acidosis complicating the administration of salicylates.

PURPOSE AND PLAN OF INVESTIGATION.

The following experimants were planned with the idea of determining whether or not the salicylates in full therapeutic doses influences the blood content of acetone bodies. Vigorous adult rabbits were used in our first series of experiments. They were narcotized by administering urethane 25% solution and chloretone saturated solution by stomach tube. Then under local anesthesia (cocaine) the trachea was canulized and attached to a Dresser respiratory apparatus; one of the carotids was canulized and connected to a mercury manometer in order to observe any flustuations in blood pressure. In none of the experiments did the blood pressure fall below 75 millimeters of mercury. The temperature of the animals was carefully noted by thermometers, and was maintained by means of artificial heat from an electrical plate.

The sodium salicylate was given intravenously in the first series of experiments with the exception of the last animal which received two grams sodium salicylate per stomach tube. Two c.c. of eight per cent aqueous solution were given in the first experiment, six c.c. in the second, and eight c.c. in the remaining experiments.

The minute volume of respired air was noted from time to time and records in the accompanying table.

A sample of blood of about five grams weight was drawn into tarred flasks, weighed and analyzed for their preformed acetone and beta-oxybutyric acid content according to Marriot's modification of Scott-Wilson's method (Jr. Biol. Chem. 0^4). The nephelometer method of estimation was used.

TABLE # 1

MINUTE VOLUME OF EXPIRED AIR.

		Time after receiving drug.							
#Expt.	Normal	15'	30'	1:00	1:30	2:00	3:00	4:00	4:30	5:00	5:30
1	680cc				690		760				
2	740		1212	1152		1108	968				
3	640		1180	980							
4	980		920	1060	1160						
5							900	920	980	765	699
6						1035	786	918	877		850

Experiment # 6 received two grams of sodium salicylate per stomach tube instead of intravenous administration.

TABLE # 2

RATE OF RESPIRATIONS PER MINUTE.

		Time after receiving drug.							
#Expt.	Normal	15'	30'	1:00	1:30	2:00	3:00	4:00	4:30	5:00
1	40				68		56			
2	52			108	116		116	124		
3	56		88	56	60					
4	48			52	56	64	68			
5								48	52	48	39

After comparing the figures in the above tables it does not appear that salicylates affect the respiratory rate or blood pressure to any appreciable extent within the time above recorded. There is an increase in the minute volume of expired air, but not so great or constant as would be looked for in specific drug action.

TABLE # 3

BLOOD ACETONE CONTENT OF RABBIT IN SALICYLATE DYSPNEA.

Milligrams of acetone per gram of blood.

Expt.	Normal	Time after receiving drug.									
		5'	10'	15'	30'	1.00	1.30	2.00	3.00	4.00	4.30	5.50
2	.02308	.01967			.0254		.02183		.02026			
3	.0329		.02802		.0214	.0301						
4	.03204			.0702		.0366		.0401				
5	.0224								.0194	.0283	.027	.0183
*6	.00862							.0262	.03614		.02978	

*The animal in Expt #6 received its salicylate per stomach tube. The blood sample withdrawn for estimation of normal was taken before the administration of the narcotic. In the preceding experiments the samples for estimation of normals were withdrawn after the animals were narcotized. The lower normal in Expt #6 maybe accounted for By the time of withdrawal in relation to the action of the anaesthetic.

TABLE # 4

BLOOD BETA-OXYBUTYRIC ACID CONTENT IN SALICYLATE DYSPNEA
Milligrams per cubic centimetre.

Expt.	Normal	Time 10'	15'	30'	1.00	2.00	3.00
3	.0336	.0334		.0464	.0395		
4	.0531		.068			.0658	
6	.0179						.0434

Comparison of the figures in the above tables reveals no apparent increase in the blood content of acetone or beta-oxybutyric acid following the drug administration.

The normal figure for beta-oxybutyric acid in Expt #6 is considerably less than the normals in the preceding experiments. It compares favorably however with later experiments, i.e. Expt #11, 13, 14, 15, and 16. The high normal values of Expt #3,4, and 5., are probably due to the action of the narcotic used in these experiments, in which the blood samples for normal estimation were drawn after the animals were full narcotized. Blood for normal in Expt #6 and later experiments were drawn before the anaesthetic was given under local anaesthesia.

In the cases of poisoning cited above the symptoms of acidosis came on after twenty-four hours from the time the salicylate was taken.

With the idea in view that the drug might affect the general metabolism so that a condition of acidosis would result after a longer, we began a second series of experiments in which the salicylate was given in toxic amount over longer periods of time.

THE EFFECTS OF EXTENDED SALICYLATE ADMINISTRATION ON THE ACETONE BODY CONTENT OF THE BLOOD.

In the experiments the blood samples were drawn under cocaine anaesthesia. After the normals were taken a large initial dose of the drug was given, followed at frequent intervals by small amounts over periods of twenty-four to forty-eight hours. The animals were kept saturated up to their lethal limit. We found 0.8 gram sodium salicylate by mouth per kilo to be the minimum lethal initial dose. Four of the animals succumbed during the course of the administration. The drug was given per stomach tube supplemented by hypodermic injection, whenever there appeared to be much gastric irritation following the use of the stomach tube.

All of these animals became very dyspneic; the breathing was first exaggerated, panting, as though after a severe exertion within two and a half to three hours after the initial dose. As the toxicity increased the respirations became slower and deeper; the animal fighting for air; irregular and gasping before death.

Convulsions usually preceded death. The rabbit inthe thirteenth experiment died forty-two hours and twenty minutes after receiving the initial dose of 0.8 gram per kilo. He had received all told by hypo and stomach tube at time of death 5.3 grams per kilo.

Samples of blood were drawn under cocaine anesthesia as soon as marked symptoms of respiratory distress and toxicity appeared, and analyzed for their acetone body content as in the previous experiments.

TABLE #5

MILLIGRAMS PREFORMED ACETONE PER CUBIC CENTIMETER BLOOD AFTER EXTENDED AND TOXIC DOSAGE OF SODIUM SALICYLATE.

#Expt.	Normal	Time after taking drug.					
		2.00	3.25	5.50	6.00	19.30	28.15
7	.0096	.0145					
8	.0157					.0136	
11	.0103				.0119		
13	.0089						.0136
14	.0180		.0101	.0128			

TABLE #6

MILLIGRAMS BETA-OXYBUTYRIC ACID PER CUBIC CENTIMETER BLOOD

AFTER EXTENDED AND TOXIC DOSAGE OF SODIUM SALICYLATE.

#Expt.	Normal	Time after taking drug. 3.25	5.50	6.00	28.15	30.25
7						
11	.0248			.02604		
13	.0182				.01603	.0222
14*	.0237	.0206	.0182			

*Experiment #14 are the figures from cats blood.

TABLE#7

RATE OF RESPIRATION

AFTER EXTENDED AND TOXIC SALICYLATE DOSAGE.

#Expt.	Normal	Time after taking drug. 1.00	3.00	3.30	4.00	6.00	7.00
11	300	320	280	200	160	120	128
13	144				118		
14	86		112		280	200	116

Examination of the results in tables # 5, 6 and 7 reveal no alteration of blood acetone body content to a degree that would produce symptoms of acidosis. The salicylate was given over a period of time long enough in this last series of experiments to determine whether or not any metabolic change produced by it was responsible for an increase in the acetone body content as noted by Langemede[1] and in the poison cases reports.

A change in the respiratory rate was brought about in all cases, which was evidently due to the central action of the drug. The low acetone body content of the blood as shown by the accompanying tables would occlude any change from possible acidosis.

A cat was used in experiment #14 on the possible assumption that a carniverous animal might respond differently than a herbiverous one. The salicylate proved to be more highly toxic to the cat than the rabbit, but the analytical results revealed no change in the acetone body content of the blood.

THE EFFECT OF SALICYLATE ADMINISTRATION ON THE ACETONE BODY CONTENT OF THE HUMAN BLOOD.

The effect of salicylate medication on the acetone body content of the blood in man was studied in one child requiring salicylates and one adult in health. The child aged nine, was given 1/3 gram sodium salicylate hourly for twenty-four hours. The adult weighing 175 pounds took one gram of sodium salicylate each hour for seventeen doses. An insignificant increase occurred in the acetone and beta-oxybutyric acid content of the child's blood, but no increase occurred in the blood of the adult. Cinchonism was caused by the salicylate in both cases.

TABLE #8

HUMAN BLOOD ACETONE CONTENT

AFTER SALICYLATE ADMINISTRATION.

#Expt.	Normal	24 hours.
*15	.0062	.00861
16	.0048	.00409
		BETA-OXYBUTYRIC ACID.
*15	.0114	.0189
16	.01714	.01343

*9 year old child.

It might be remarked that the blood of the child showed a tendency to increase the acetone and beta-oxybutyric acid in content. Possibly this may be accentuated in some cases.

CONCLUSION.

Salicylate circulating in full therapeutic or toxic doses in the blood does not alter the acetone, diacetic acid or beta-oxybutyric acid content of the blood in man or rabbit.

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