EXPERIMENTAL STUDIES OF THE VALIDITY OF ADVERTISED CLAIMS FOR PRODUCTS OF PUBLIC IMPORTANCE IN RELATION TO ORAL HYGIENE OR DENTAL THERAPEUTICS

6. MAY THE USE OF PEBECO TOOTH-PASTE, TWICE A DAY, BE REASONABLY REGARDED AS A PART OF "THE BASIS OF CORRECT ORAL HYGIENE?"

PART II. TESTS OF THE RELATIVE TOXICITY OF POTASSIUM CHLORATE AFTER INTRAVENOUS INJECTION INTO ALBINO RATS

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I. INTRODUCTION

The manufacturers of Pebeco Tooth-Paste have advertised the claim that the use of that paste as a dentifrice, "twice a day," is a part of "the basis of correct oral hygiene" (3). Distinguished physicians and dentists have denied the validity of this claim in behalf of the use of Pebeco as a dentifrice, on the ground that potassium chlorate (present in Pebeco to the amount of 50 per cent) is "an extremely dangerous drug, death often resulting from its unguarded use," and that "grave perils attend the employment" of dentifrices, such as Pebeco, that contain potassium chlorate in large proportions (3).

It is obvious that, if potassium chlorate is an "extremely dangerous drug" and if Pebeco Tooth-Paste contains 50 per cent of it, the denti-

frictional use of Pebecco, "twice a day," cannot be truthfully advertised as a part of "*the basis of correct oral hygiene.*"

In an effort independently to ascertain the facts in this situation, and to do so on the basis of experimental findings, I have been conducting an investigation of the toxicity of potassium chlorate, determined directly and in comparison with the toxicity of various familiar substances of either physiologic or toxicologic import, or both, such as sodium chloride, potassium sulfocyanate, and mercuric chloride. *Part I* of this study presented the results of "preliminary tests of the relative toxicity of potassium chlorate for tadpoles and newts" (1). In the tests there described, the animals were kept continuously immersed in solutions of potassium chlorate or of substances with which the toxicity of potassium chlorate was compared. It was concluded, judging from the mortality records of the tests, that "potassium chlorate was somewhat more toxic than common salt, but much less poisonous than common soaps or sodium arsenite, and very much less destructive than mercuric chloride; it was also less damaging than potassium sulfocyanate."

These results for tadpoles and newts cannot be arbitrarily applied to human conditions. The results do indicate, however, that, for man, potassium chlorate is not as "*dangerously*" poisonous, and that its dentifricial use is not as "*gravely*" perilous, as has been believed; but, of course, these findings do not show that potassium chlorate is not a poison or that potassium chlorate may be taken into the body with impunity. The results suggest, and prepare the way for, an extension of the experiments.

In this, the second, part of this investigation, an effort was made to obtain results for the absolute and relative toxicities of potassium chlorate that would be more sharply defined mathematically than those of *Part I*; that would show effects after direct introduction into the blood; and that would relate to a type of animal more nearly allied to man. Accordingly, solutions of potassium chlorate and comparable substances were injected intravenously into a hundred albino rats, under conditions that have yielded results of special value and significance.

II. EXPERIMENTAL (PLAN, METHODS)

Plan

Part I of this series of studies was directed primarily at the question of the *absorbability* of potassium chlorate (1). It was said in this relation (page 315): "One of the most important considerations involved in the toxicology of potassium chlorate, as an ingredient of dentifrices, is the question of its *absorbability through the oral mucous membranes*. Does potassium chlorate, introduced into the mouth in the form, say, of Pebeco, pass into and through the oral mucous membranes in sufficient quantity, at a time or in time, to damage the membranes (and injure the person)? This question presents the crux of the whole problem under review." It was believed, at the outset, that the results of comparative tests of the toxicity of potassium chlorate and other substances, on tadpoles and newts continuously immersed in solutions of these substances, would show clearly that potassium chlorate is or is not readily absorbable into the blood through membranes similar to those in the human mouth, and that potassium chlorate is or is not an "*extremely*" poisonous substance after its passage by absorption into the blood. The findings indicate, in a general way, that although potassium chlorate is readily absorbable and also toxic, it is not, as has already been said, as dangerously poisonous as some believe it to be (3).

Toxicologic results for a given species may not apply with equal significance to other species. A fair objection to the application of the results obtained with tadpoles and newts, to *human* conditions, is the *possibility* that tadpoles and newts are relatively less susceptible than men to the action of potassium chlorate. (Of course, on the other hand, they may be more so.) It is *possible* that these cold-blooded animals are materially different from men in the comparative degrees, conditions, and rates, of their absorption of potassium chlorate, even under the most favorable conditions for its transmission to the blood, and that, therefore, the results for tadpoles and newts mean less (or more, of course), for men, than they seem. It is *conceivable*, also, that such cold-blooded animals do not show the *degree* of injury they would if potassium chlorate were absorbed into their blood (in such experiments as those described in Part I), in the man-

ner and to the extent that it is absorbed in men (presumed here for the sake of judicial argument), *from the mouth*, or stomach, or both, when Pebecco and similar products are used as dentifrices.

In order to resolve these doubts, however extreme they may be, and also to extend the scope and deepen the import of this investigation, (a) the question of *absorbability* into the blood was entirely removed from consideration, for the time being, by the simple expedient of injecting solutions of the compared substances *directly into the circulating blood itself*, (b) and a higher type of animal—the albino rat—used for the purpose. This animal, an omnivorous mammal, unlike the tadpole or newt, closely resembles man in dietary habits, nutritive character, physiological quality, and toxicologic responsiveness; and affords a more conventional basis for the determination of toxicologic properties that are applicable to, and demonstrable in, man.

Experiments on men will be postponed until it is certain that potassium chlorate is either so poisonous that such experiments would be unjustifiable, in which event they would not be attempted; or so innocuous, that adequate experiments in this relation would not be dangerous in any degree and could be conducted with entire fairness to the individuals involved.

The literature on the toxicology of potassium chlorate will be reviewed with the discussion of a later series of findings, when all the available facts can be summarized to the greatest advantage.

Methods

Animals. The animals used in these tests were selected from our own colony of albino rats, which has been in process of *continuous* development in this laboratory for a period of seven years. The colony has been developed for the routine and experimental work of this laboratory. Only the healthiest adults have been used for breeding purposes and abnormal rats of all ages have been promptly chloroformed. As a consequence (the animals having been given an abundance of good food and fresh water daily, and confined in suitable cages that have been cleaned once a day), the available rats in the colony are notable for their uniform vigor and outstanding normality—"survivals of the fittest" as well as of the most suitable for such experiments as those described below.

Diet. From the beginning of their independent nutritive existence, the rats were fed daily an abundance of good "balanced" food, on the following weekly dietary schedule: *Sunday*—fresh cabbage, cheese; *Monday*—cracked corn, beef-heart; *Tuesday*—milk, wheat bread; *Wednesday*—fresh cabbage, beef-heart; *Thursday*—fresh turnip, cheese; *Friday*—rye grain, wheat bread; *Saturday*—oats, beef-heart. The rats were also fed on this dietary schedule immediately after a series of injections was completed, and thereafter to the end of the period of observation.

Chemicals employed. The best available chemical preparations were used in the injections. With the exception of the soaps (see foot-note in *table 1*), all the products were Eimer and Amend "*tested purity*," or Kahlbaum "*K*," preparations. The portions of the products intended for the solutions to be used in the injections were taken from previously unopened containers, and were weighed directly as removed therefrom. No attempt was made to eliminate atmospheric moisture from the mass of the product to be weighed, but all due care was taken to prevent introduction of moisture and impurities. All the products were dry; and any error due to original inclusion of atmospheric moisture, in the weights of products taken, must certainly have been within the range of influence of the unpreventable variations in the animals themselves—variations without material bearing on the significance of results ("average") obtained for a relatively large number of animals, as was the case for each substance tested in this work. The solutions prepared for the injections (4 to 16 per cent) were made in volumes of 100 cc.

Injection technic. The injection procedure was identical in principle, and in most details, with that required by the U. S. Government for official tests, on albino rats, of the toxicity of arsphenamine (Salvarsan). It was modified in non-essentials to meet certain desirabilities in these tests and conducted as follows:

From twelve to fifteen hours prior to the times at which the individual injections were to be made (the requirement in the official method above referred to is twelve to eighteen hours), the well nourished rats selected for a given test were removed from cages containing an abundant supply of food and water to one containing no food but an abundance of water. (This precaution prevents disturbing variations in weight, and consequent errors in the calculations of dosage for the subsequent injections, that might otherwise be introduced by inequalities in the amounts of food in the alimentary tracts of the animals involved.) Just before a series of injections was started the animals to be treated were carefully weighed in grams, the weights recorded in the nearest whole numbers (maximum deviation, 0.5 gram), and the rats put temporarily into small individual cages. (Neither food nor water was given during this short period.)

One rat after another was then fastened, outstretched on its back, on an ordinary holder (not too tightly to interfere with respiration); the hair removed from the inside surface of the upper right hind leg, with a barium sulfid-soap-flour-talcum-water mixture; the saphenous vein exposed by a suitable superficial incision (without the aid of an anesthetic, as required in the official method mentioned above); and the calculated volume of solution then carefully and visibly injected, in toto, into that vein with a minutely and accurately calibrated Luer syringe, with a very fine needle, from which deliveries of 0.01 cc. could be made completely and continuously under control. The injections were made as closely and as uniformly as possible at a rate of 0.1 cc. of solution in 15 seconds, the rate rarely becoming more rapid than 13 seconds nor slower than 17 seconds, and averaging 15 seconds, per 0.1 cc. of solution.

Immediately after the completion of the injection in each case, the wound was closed with a single stitch of silk thread, and the rat isolated in a small cage until the remaining injections were concluded. In every instance in which an animal survived the injection, the wound over the saphenous vein healed rapidly and uneventfully.

Hemorrhage from the vein and wound was always insignificant—frequently it did not occur.

Period of observation. The surviving animals for a given test, after being suitably marked for individual identification, were assembled in one cage and kept there until the end of the period of observation—at least two weeks in every instance. With them in the same or near-by cages, “control” (untreated) animals of the same age, size, and sex were closely associated, to afford direct comparisons of treated with normal untreated animals, and thus to guard against misinterpretations of any unexpected or unaccountable deviations in condition (none of which arose).

The tests were conducted, from time to time, during the months of June, July and August.

III. SUMMARY OF THE RESULTS

Tabulated data. The mortality record and further details of the tests are shown in *table 1*.

Table 1 gives the essential data for each substance named in the sectional headings (I–VII). For each group of tests, in sub-sections A to V, is stated (a) the kind of product employed in the corresponding test; (b) the concentration of the solution injected; (c) the sex of the

individual rats; (d) the length of the period immediately preceding the injections during which the previously well-fed animals were continuously deprived of food (with water always available); and (e) the added length of the injection period during which neither food nor water was received by the rats prior to their replacement in cages where food for the day, and water, were freely available. (The total amount of time involved in conditions "d" and "e," above, is the length of the period during which no food had been received by the rat *last* treated.)

The columns in *table 1*, as shown by the general headings, give (a) the sequence numerals of record for the individual rats; (b) the weights of the rats in grams taken a few minutes before the beginning of the injection period for the corresponding groups; (c) the volumes of solution injected into the individual rats, expressed in tenths of cubic centimeters ("cc./10"); (d) the actual amounts of the tested substances contained in the injected volumes ("total dose"), expressed in milligrams; (e) the amounts of the substances thus injected, calculated per kilo of the body-weights of the corresponding rats ("dose per kilo"), expressed in milligrams; and (f) indications of the toxic results, after the injections, expressed to indicate survival ("+") to the end of the *shortest* period of observation (two weeks), or death ("—") *within* the number of minutes, after the *completion* of the injections, specified by the corresponding numerals.

Miscellaneous additional data. Each group of treated animals that survived, and all the control rats, weighed more at the end of the period of observation than they did at the time the corresponding injections were made. As this general statement presents the essential facts in this relation, all the weights for control animals, and for the groups of treated animals at the ends of the tests, are omitted from the printed record, as non-significant.

All the animals that survived were lively and vigorous at the ends of the periods of observation, a fact showing clearly that the large tolerated doses did not exercise cumulative or continuing toxic effects.

The toxic symptoms, in the tests that terminated fatally, were such as are characteristic of the substances injected. Death through the action of the largest doses of *sodium chloride* and *sodium chlorate* was attended by convulsions, and by edema of the lungs with extrusion of froth from the nostrils. Cyanosis to a marked degree

TABLE 1

Data pertaining to the comparative toxicity of potassium chlorate, sodium chloride, potassium sulfocyanate, sodium nitrite, potassium chloride, sodium chlorate, and soaps (castile and sodium oleate), after their respective intravenous injection into albino rats

RAT		DATA PERTAINING TO THE INJECTIONS			RESULTS	
Number	Weight, grams	Volume injected, cc./10	Dose injected		Lived 2 weeks	Died: min.
			Total, mgm.	Per kilo, mgm.		

I. Potassium chlorate

A. Potassium chlorate (Eimer and Amend, "tested purity"): 4 per cent solution. Male rats. Food not available for 12 hr., 10 min., prior to the first injection. Length of the period during which the five injections were made: 52 min.

1	189	12.2	48.8	258	—	4
2	176	10.6	42.4	241	+	
3	175	8.8	35.2	201	+	
4	172	11.0	44.0	256	+	
5	149	9.5	38.0	255	+	

B. Potassium chlorate (Eimer and Amend, "tested purity"): 4 per cent solution. Male rats. Food not available for 12 hr., 30 min., prior to the first injection. Length of the period during which the five injections were made: 58 min.

6	222	14.4	57.6	260	+	
7	213	13.9	55.6	261	+	
8	212	14.9*			+	
9	206	14.4	57.6	280	+	
10	200	14.0	56.0	280	+	

C. Potassium chlorate (Kahlbaum, "K"): 4 per cent solution. Female rats. Food not available for 12 hr., 47 min., prior to the first injection. Length of the period during which the six injections were made: 1 hr., 8 min.

11	100	7.0	28.0	280	—	1
12	101	7.1	28.4	281	—	1
13	107	7.0	28.0	262	—	2
14	108	6.8	27.2	252	+	
15	111	6.9	27.6	249	+	
16	128	8.0	32.0	250	+	

D. Potassium chlorate (Kahlbaum, "K"): 4 per cent solution. Male rats. Food not available for 12 hr., 15 min., prior to the first injection. Length of the period during which the five injections were made: 1 hr., 20 min.

17	180	12.6	50.4	280	+	
18	198	14.4	57.6	291	+	
19	200	14.5	58.0	290	+	
20	223	16.0	64.0	287	+	
21	231	17.4	69.6	301	—	1

* Distilled water instead of potassium chlorate solution was injected into rat 8. There were no observable effects of either the water or the volume.

TABLE 1—Continued

Data pertaining to the comparative toxicity of potassium chlorate, sodium chloride, etc.

RAT		DATA PERTAINING TO THE INJECTIONS			RESULTS	
Number	Weight, grams	Volume injected, cc. / 10	Dose injected		Lived 2 weeks	Died: min.
			Total, mgm.	Per kilo, mgm.		

II. Sodium chloride

E. Sodium chloride (Kahlbaum, "K"): 4 per cent solution. Male rats. Food not available for 12 hr., 35 min., prior to the first injection. Length of the period during which the six injections were made: 1 hr., 15 min.

22	196	12.8	51.2	261	+	
23	189	13.3	53.2	281	+	
24	179	13.4	53.6	299	+	
25	178	15.1	60.4	339	+	
26	169	14.8	57.6	350	+	
27	165	14.9	59.6	361	+	

F. Sodium chloride (Kahlbaum, "K"): 8 per cent solution. Female rats. Food not available for 13 hr., 15 min., prior to the first injection. Length of the period during which the five injections were made: 48 min.

28	105	7.4	59.2	564	+	
29	101	8.1	64.8	642	+	
30	100	9.0	72.0	720	+	
31	95	10.5	84.0	884	+	
32	95	12.4	99.2	1,044	+	

G. Sodium chloride (Kahlbaum, "K"): 16 per cent solution. Female rats. Food not available for 13 hr., 25 min., prior to the first injection. Length of the period during which the four injections were made: 40 min.

33	103	8.3	132.8	1,289	+	
34	94	13.7	219.2	2,332	—	1
35	97	13.6	217.6	2,243	+	
36	151	22.7	363.2	2,405	—	8

III. Potassium sulfocyanate

H. Potassium sulfocyanate (Eimer and Amend, "tested purity"): 4 per cent solution. Male rats. Food not available for 13 hr., 55 min., prior to the first injection. Length of the period during which the five injections were made: 58 min.

37	196	4.7	18.8	96	+	
38	186	4.7	18.8	101	+	
39	186	5.6	22.4	120	+	
40	181	6.4	25.6	141	—	2
41	164	5.1	20.4	124	+	

TABLE 1—Continued

Data pertaining to the comparative toxicity of potassium chlorate, sodium chloride, etc.

RAT		DATA PERTAINING TO THE INJECTIONS			RESULTS	
Number	Weight, grams	Volume, injected, cc./10	Dose injected		Lived 2 weeks	Died: min.
			Total, mgm.	Per kilo, mgm.		

III. Potassium sulfocyanate—Continued

I. Potassium sulfocyanate (Kahlbaum, "K"): 4.0 per cent solution. Female rats. Food not available for 12 hr., 45 min., prior to the first injection. Length of the period during which the three injections were made: 34 min.

42	109	3.3	13.2	121	+	
43	103	3.6	14.4	140	+	
44	101	3.8	15.2	150	—	1

IV. Sodium nitrite

J. Sodium nitrite (Eimer and Amend, "tested purity"): 4 per cent solution. Male rats. Food not available for 12 hr., 30 min., prior to the first injection. Length of the period during which the five injections were made: 1 hr., 8 min.

45	211	14.8	59.2	281	—	5
46	214	12.9	51.6	241	—	10
47	222	8.9	35.6	160	—	18
48	190	3.8	15.2	80	—	45
49	188	4.7	18.8	100	—	27

K. Sodium nitrite (Kahlbaum, "K"): 4.0 per cent solution. Male rats. Food not available for 13 hr., 55 min., prior to the first injection. Length of the period during which the four injections were made: 47 min.

50	161	3.3	13.2	82	—	43
51	183	2.8	11.2	61	+	
52	193	2.0	8.0	41	+	
53	206	4.1	16.4	80	—	21

V. Potassium chloride

L. Potassium chloride (Kahlbaum, "K"): 4.0 per cent solution. Male rats. Food not available for 12 hr., 30 min., prior to the first injection. Length of the period during which the six injections were made: 54 min.

54	113	3.9	15.6	138	—	2
55	108	3.8	15.2	141	—	1
56	104	2.6	10.4	100	+	
57	101	3.0	12.0	119	+	
58	100	3.3	13.2	132	+	
59	99	3.2	12.8	129	+	

TABLE 1—Continued

Data pertaining to the comparative toxicity of potassium chloride, sodium chloride, etc.

RAT		DATA PERTAINING TO THE INJECTIONS			RESULTS	
Number	Weight, grams	Volume, injected, cc./10	Dose injected		Lived 2 weeks	Died: min.
			Total, mgm.	Per kilo, mgm.		

V. Potassium chloride—Continued

M. Potassium chloride (Kahlbaum, "K"): 4 per cent solution. Female rats. Food not available for 13 hr., 5 min., prior to the first injection. Length of the period during which the four injections were made: 46 min.

60	204	6.6	26.4	129	+	
61	180	6.3	25.2	140	—	1
62	197	6.4	25.6	130	+	
63	175	6.1	24.4	139	—	2

VI. Sodium chloride

N. Sodium chloride (Eimer and Amend, "tested purity"): 4 per cent solution. Female rats. Food not available for 12 hr., 40 min., prior to the first injection. Length of the period during which the five injections were made: 48 min.

64	106	8.5	34.0	321	+	
65	104	10.4	41.6	400	+	
66	98	11.8	47.2	482	+	
67	93	13.0	52.0	559	+	
68	94	15.1	60.4	643	+	

O. Sodium chloride (Eimer and Amend, "tested purity"): 8 per cent solution. Female rats. Food not available for 12 hr., 35 min., prior to the first injection. Length of the period during which the five injections were made: 1 hr., 5 min.

69	108	7.6	60.8	563	+	
70	106	9.6	76.8	725	+	
71	100	12.0	96.0	960	+	
72	93	13.0	104.0	1,118	+	
73	89	14.3	114.4	1,285	+	

P. Sodium chloride (Eimer and Amend, "tested purity"): 16 per cent solution. Female rats. Food not available for 12 hr., 38 min., prior to the first injection. Length of the period during which the seven injections were made: 1 hr., 12 min.

74	96	7.7	123.2	1,283	+	
75	90	9.0	144.0	1,600	+	
76	88	10.6	169.6	1,927	+	
77	86	12.1	193.6	2,251	+	
78	86	13.8	220.8	2,567	+	
79	85	14.5	232.0	2,729	—	3
80	85	13.6	217.6	2,560	+	

TABLE 1—Continued

Data pertaining to the comparative toxicity of potassium chlorate, sodium chloride, etc.

RAT		DATA PERTAINING TO THE INJECTIONS			RESULTS	
Number	Weight, grams	Volume injected, cc./10	Dose injected.		Lived 2 weeks	Died: min.
			Total, mgm.	Per kilo, mgm.		

*VII. Soaps (castile and sodium oleate)**

Q. Soap (castile: Eimer and Amend): 4 per cent solution. Male rats. Food not available for 13 hr., 44 min., prior to the first injection. Length of the period during which the two injections were made: 16 min.

81	182	5.8	23.2	127	—	1
82	178	2.7	10.8	61	+	

R. Soap (castile: Eimer and Amend): 4 per cent solution. Female rats. Food not available for 13 hr., 35 min., prior to the first injection. Length of the period during which the three injections were made: 25 min.

83	104	2.4	9.6	92	+	
84	103	3.1	12.4	120	+	
85	97	6.8	27.2	280	—	7

S. Soap (castile: Eimer and Amend): 4 per cent solution. Male rats. Food not available for 14 hr., 15 min., prior to the first injection. Length of the period during which the three injections were made: 21 min.

86	99	5.0	20.0	202	—	1
87	96	3.9	15.6	163	—	2
88	96	2.9	11.6	121	—	2

T. Soap (castile: Eimer and Amend): 4 per cent solution. Female rats. Food not available for 13 hr., 55 min., prior to the first injection. Length of the period during which the two injections were made: 16 min.

89	91	2.7	10.8	119	+	
90	91	2.7	10.8	119	+	

U. Soap (sodium oleate: Eimer and Amend): 4 per cent solution. Female rat. Food not available for 14 hr., 5 min., prior to the injection.

91	102	3.1	12.4	122	+	
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* The castile soap and sodium oleate used in tests Q to V, inclusive, were the best commercial products available. *The preparations were certainly similar to, and as pure as, the soaps used in dentifrices.* The products dissolved so completely in water (4 per cent) that practically no appreciable mathematical variation was introduced by the filtration of the solutions. In an extension of this phase of the work, purer products will be purchased or prepared, and additional results obtained and published. The influence of the kinds and degrees of alkalinity of the soap solutions employed will also be studied in this relation and the data reported with those for toxicity.

TABLE 1—*Concluded**Data pertaining to the comparative toxicity of potassium chlorate, sodium chloride, etc.*

RAT		DATA PERTAINING TO THE INJECTIONS			RESULTS	
Number	Weight, grams	Volume injected, cc. /10	Dose injected		Lived 2 weeks	Died: min.
			Total, mgm.	Per kilo, mgm.		

*VII. Soaps (castile and sodium oleate)—Continued**

V. Soap (castile, Eimer and Amend, rats 92-94; sodium oleate, Eimer and Amend, rats 95-101): 4 per cent solution. Sex of the rats: 92-97, female; 98-101, male. Food not available for 12 hr., 21 min., prior to the first injection. Length of the period during which the ten injections were made: 2 hr., 2 min.

92	92	3.2	12.8	139	—	1
93	92	3.0	12.0	130	—	1
94	90	2.7	10.8	120	+	
95	86	2.8	11.2	130	+	
96	85	3.0	12.0	141	+	
97	83	2.7	10.8	130	—	2
98	106	3.5	14.0	132	+	
99	103	3.6	14.4	140	+	
100	101	3.8	15.2	150	—	1
101	96	3.3	13.2	138	+	

* See the foot-note on the opposite page.

(and convulsions also for the largest doses) occurred after the treatments with *sodium nitrite*, but normal color was gradually restored in a few hours in each of the survivors.

The lethal doses of *soaps*, *potassium chloride*, *potassium sulfocyanate*, and *potassium chlorate*, promptly caused death attended by convulsive movements. After fatal treatment with soap, there was usually a series of convulsive movements followed by cessation of respiration for from fifteen to thirty seconds, or a little longer, then resumption of shallow breathing for a few seconds, then death.

Some of the largest *non-lethal* doses of each of these substances suddenly appeared to be causing death before the calculated volumes had been fully injected, in which instances the injections were then stopped immediately, in the belief that death was imminent; and, of course, only the volumes actually injected are recorded in the table. These striking results, very near the "death line," made it possible

all the more satisfactorily to establish the approximate lethal dose of each of these substances, for albino rats, under the conditions of the tests.

IV. DISCUSSION OF THE RESULTS

The many individual results, recorded in *table 1*, are conveniently reduced to simple terms in *table 2*, which presents a summary of mathematical data for the "minimal lethal dose" and for the "maximum tolerated dose," for each substance, expressed in milligrams per kilo of body-weight of rat, and arranged in the order, downward, of indicated greatest toxicity to indicated least toxicity:

TABLE 2

A summary of data for "minimal lethal doses" and "maximum tolerated doses," in albino rats, for the substances named in table 1

SUBSTANCE TESTED	MINIMAL LETHAL DOSE PER KILO	MAXIMUM TOLER- ATED DOSE PER KILO
	mgm.	mgm.
Sodium nitrite	80	61
Castile soap	121	120
{ Sodium oleate (soap)	{ 130	{ 141
{ Potassium chloride	{ 138	{ 132
{ Potassium sulfocyanate	{ 141	{ 140
Potassium chlorate	258	291
Sodium chloride	2,332	2,243
Sodium chlorate	2,729	2,567

The essential results of the tests described in this paper are shown pointedly by the general data in *table 2*. Injected directly at a standard rate into the venous circulation of albino rats, under uniform nutritive and environmental conditions, potassium chlorate, "*milligram for milligram*," obviously was markedly *less toxic* than such substances of physiological occurrence as sodium nitrite, soaps, potassium chloride or potassium sulfocyanate, but was very much *more toxic* than sodium chloride or sodium chlorate.

The results, considered from special points of view, suggest that much of the toxicity of potassium chlorate is due to its potassium. The data for *potassium* chloride on one side (more toxic), and for *sodium* chlorate on the other (less toxic), strongly support this inference.

These results raise a new question, namely: if *potassium* chlorate is useful in a dentifrice, why would not *sodium* chlorate be more useful, since sodium chlorate is much less poisonous than potassium chlorate (and even less poisonous than an equal weight of sodium chloride), and presumably would exercise the beneficial influence that now is ascribed to potassium chlorate in dentifrices. This question will be raised again, in a later communication.

In the introductory part of this paper it was said that one of the reasons for conducting tests on animals higher in type than those used in Part I of this study was the obvious possibility that the results for toxicity on tadpoles and newts were not representative of relative effects on mammals. We see, however, that instead of divergence there is striking agreement between the general results on rats and the comparable data for tadpoles and newts.

If the comparable data for tadpoles and newts (Part I) are summarized in a manner similar to that shown in *table 2*, the arrangement presented in *table 3* is obtained.

TABLE 3

A summary of data for "minimal lethal doses" and "maximum tolerated doses," in tadpoles and newts, for the substances tested in Part I (1)

SUBSTANCE TESTED	MINIMAL LETHAL DOSE	MAXIMUM TOLERATED DOSE
	<i>per cent</i>	<i>per cent</i>
<i>For tadpoles</i>		
Soap.....	0.02 (2 hours)	
Potassium sulfocyanate.....	0.10 (51 hours)	
Potassium chlorate.....	0.10 (14 days)	0.4 (31 days)
Sodium chloride.....	0.20 (6 days)	1.0 (7 days)
<i>For newts</i>		
Soap.....	0.02 (20 hours)	
Potassium sulfocyanate.....	*	
Potassium chlorate.....	0.40 (10 days)	1.5 (5 days)
Sodium chloride.....	(above 1.0 for 7 days)	1.0 (7 days: the highest tried)

* Not tested on newts.

The sequence of toxicity shown by the data in the foregoing summary (proceeding from the substance of greatest indicated toxicity to that of the least), is, for *tadpoles*: soap > potassium sulfocyanate >

potassium chlorate > sodium chloride; for *newts*: soap > (potassium sulfocyanate not tested) > potassium chlorate > sodium chloride—the sequence, in each case, for these substances in the summary of the data for rats.

These agreements do not encourage or support the opinion that possibly different relative toxicities would be shown by these substances in men.

The mathematical data have been considered here on a gravimetric basis alone. If toxicity were estimated from calculations of the data on a molecular basis, however, the sequential position of potassium chlorate would be the same; the soaps would exchange places with sodium nitrite as the most poisonous; and sodium chloride would exchange places with sodium chlorate as the least toxic. There would be little significant alteration in the positions of the others in the sequence noted above. After further progress will have been made in this work, all the mathematical data of Part I, and of this part and of the parts to follow, will be compared from both the gravimetric and molecular points of view, and discussed accordingly.

The conspicuous toxicity of soaps, both in Part I and in this part of the study, automatically raises the question whether the introduction of soaps into the mouth, in dentifrices, is as harmless *for the gums* as has been generally believed. Certainly nothing in this work, so far, suggests that the repeated presence of large quantities of soap in the mouth is a matter of hygienic indifference. Special attention will be given to this phase of the subject in a future communication.

The results have an unexpected bearing on the “old sulfocyanate question.” It was shown in this laboratory, some years ago (2), that sulfocyanate in the saliva is a waste product and that it has no relation to the incidence or progress of dental caries. The data for toxicity of potassium sulfocyanate seem to support the finding that sulfocyanate is wholly an excretory (waste) product and not in any sense a secretory (useful) substance. Results of special comparative tests with *sodium* sulfocyanate and other sulfocyanates, however, to determine whether or not the toxicity of *potassium* sulfocyanate is due mainly to its *potassium*, or to its sulfocyanate radical, will be required before the later results can be regarded as certainly confirmatory of the earlier. The results of such tests will be published in a future issue of this JOURNAL.

Nitrite as a constituent of saliva is seen to be in a position analogous to that of salivary sulfocyanate. The results of these tests suggest a special study of the origin of nitrite in the body, the quantities of its elimination in saliva, the significance of variations in its salivary and urinary excretions, the possibility of an important natural relation of nitrite to nervous and vasomotor phenomena, and the quantity of nitrite in saliva as an index of such relationships. Such studies will be undertaken.

It was stated, in the summary of results for Part I of this series of studies, that the danger of poisoning in the dentifricial use of potassium chlorate is "not as great as some of the clinical data in the toxicological records suggest," and that potassium chlorate is neither an "*extremely*" dangerous drug nor a "*gravely*" poisonous substance. The results of the tests described in the present paper confirm this conclusion (with emphasis on the words italicized).

The questions whether potassium chlorate, *when taken into the mouth or stomach*, or both, in the form of, say, Pebeco, is absorbed into the blood rapidly enough, and in sufficient proportions, to injure the person, have not been touched directly either in Part I or in the present paper. The experiments comprising Part III, which bears directly on these particular questions, have already been completed and will be described in the succeeding issue of this JOURNAL.

The toxicity of potassium chlorate has been compared in these tests, in the main, with that of comparatively non-toxic or weakly toxic substances. In a subsequent communication will be published the results of a similar study of the toxicity of potassium chlorate compared with that, in albino rats, of such poisons as ordinary salts of mercury, lead, and copper.

Direct response to the question in the title of this paper will follow the presentation of the results of the concluding experiments. It is believed that, by that time, the experimental results will have afforded sufficient evidence to provide a completely truthful answer.

V. GENERAL CONCLUSIONS

In normal albino rats, under uniform dietary and environmental conditions, and injected intravenously, at a standard rate, in aqueous solutions of equipercantage concentration, potassium chlorate was

markedly *less toxic* than sodium nitrite, castile soap, sodium oleate, potassium chloride, or potassium sulfocyanate, but was very much *more toxic* than sodium chloride or sodium chlorate.

The sequence of toxicity for the substances tested, under the conditions stated above, proceeding in order from the substance of greatest toxicity to that of least toxicity, was the following: (a) sodium nitrite, (b) castile soap, (c) sodium oleate = potassium chloride = potassium sulfocyanate, (d) potassium chlorate, (e) sodium chloride, (f) sodium chlorate.

The sequence of toxicity in the results for rats was the same as that (for the substances in both groups) in previous toxicity tests on tadpoles and newts (1).

The relative non-toxicity of sodium chlorate raises the question whether any benefits that may accrue from the dentifricial use of *potassium* chlorate cannot be more advantageously derived from the use, instead, of the much less poisonous *sodium* chlorate.

The results confirm the conclusion previously stated (1), that potassium chlorate is not an "extremely" dangerous drug and that its dentifricial use is not "gravely" perilous, although the findings do not suggest that potassium chlorate may be taken into the body indifferently, or that its use in dentifrices is desirable.

VI. LITERATURE CITED

- (1) GIES, WM. J. 1920 Experimental studies of the validity of advertised claims for products of public importance in relation to oral hygiene or dental therapeutics. 5. May the use of Pebecco Tooth-Paste, twice a day, be reasonably regarded as a part of the basis of correct oral hygiene?—Part I: *Preliminary tests of the relative toxicity of potassium chlorate for tadpoles and newts*. JOURNAL OF DENTAL RESEARCH, ii, p. 313.
- (2) KAHN, MAX, and GIES, WM. J. 1912 An inquiry into the possible relation of sulfocyanate to dental caries. *Transactions of the Dental Society of the State of New York*, p. 150 (*Dental Cosmos*, 1913, lv, p. 40).—LIEB, C. C., KAHN, MAX, and GIES, WM. J. 1913. A further study of sulfocyanate in its possible relation to dental caries. *Ibid.*, p. 142 (*Dental Cosmos*, 1914, lvi, p. 173).
- (3) TAYLOR, J. M., GREELEY, H., LIMERICK, O. V., MERRITT, A. H., STILLMAN, P. R., HYATT, T. P., BUCKLEY, J. P., and CARNEY, M. F. 1919 Highfalutin dupery: Comment on the falsity of various published claims for certain dentifrices. JOURNAL OF DENTAL RESEARCH, i, p. 503.

CUMULATIVE SUMMARY OF FINDINGS¹

*Mennen's Cream Dentifrice.*² Not acid in reaction as advertised, but alkaline. Therefore, claims of beneficial action, when used as a dentifrice, as *due to acidity*, are wholly unwarranted. Karshan and Gies: JOURNAL OF DENTAL RESEARCH, 1920, ii, p. 293.

Pebeco Tooth-Paste (and other dentifrices containing potassium chlorate). The opinion recently expressed by Taylor, Greeley, Limerick, Merritt, Stillman, Hyatt, Buckley, and Carney (JOURNAL OF DENTAL RESEARCH, 1919, i, 503), to the effect that potassium chlorate is an "*extremely dangerous drug*" and that "*grave perils attend the employment*" of dentifrices such as Pebeco (which contains potassium chlorate in very large proportion), seems to be an overemphasis on the facts of toxicity. Tests of relative toxicity, on tadpoles and newts by the immersion method and on albino rats by intravenous injection, show that such substances of ordinary physiological occurrence as sodium nitrite, castile soap, sodium oleate, potassium chloride, and potassium sulfocyanate, are markedly more toxic than potassium chlorate, but that the latter is much more poisonous than common salt or sodium chlorate. *Sodium* chlorate, per unit of weight, is less toxic than sodium chloride. The use of the more toxic *potassium* chlorate in preference to the non-toxic *sodium* chlorate, as a constituent of dentifrices, remains to be explained. Gies: JOURNAL OF DENTAL RESEARCH, 1920, ii, pp. 313 and 511.

*Pepsodent.*² Contrary to advertised claims, Pepsodent, used as a dentifrice, *does not* (a) completely remove mucin plaques from teeth, or (b) effectively prevent re-formation of such plaques on teeth, *by a digestive action of contained pepsin "activated" by admixed acid calcium phosphate*. "Pepsodent Bulletin No. 4" presents nothing to support this advertised claim, or to show any error in the denial of the validity of this claim. (1) Gies: *Journal of the American Medical Association*, 1917, lxxviii, p. 1278 (reprinted in the JOURNAL OF DENTAL RESEARCH, 1919, i, p. 507); (2) Franke and Gies: *Journal of the Allied Dental Societies*, 1917, xii, p. 360; (3) Franke and Gies: JOURNAL OF DENTAL RESEARCH, 1919, i, p. 511; (4) Gies: *Ibid.*, 1920, ii, p. 299.

¹ A cumulative summary of findings is appended to each of the papers in this series. This plan enables us to present, recurrently, the *sum* of the findings in this series of investigations.

² The only findings, known to the authors named at the end of the note, that support the claims referred to, have been published solely in advertisements.