ideal process, and hoped that Dr. Beal's method may prove to be well adapted, for example, in the determination of morphine in tablets.

Mr. L. E. Warren said if future results show up as satisfactory as indicated, this will prove the most important contribution to alkaloidal science since the discovery of Lloyd's reagent. He asked whether the reagent was adaptable to the recovery of alkaloids from plant extracts on a large scale.

To the first question, Dr. Beal replied he thought by a modification of the method it would prove satisfactory in the morphine determination; the results in belladonna by this method checked within two or three hundreths of one per cent.

In reply to the other question, Dr. Beal thought the method was applicable; he had separated pure strychnine in toxicological work.

TOXICITY OF QUININE-ASPIRIN MIXTURE.*

BY E. A. RUDDIMAN AND C. F. LANWERMEYER.

From time to time articles have appeared in pharmaceutical and medical journals relative to the toxicity of mixtures of quinine salts with organic acids. Professor Biddle (*Journal Am. Chem. Soc.*, XXXIV, 500, 1912) states that salts of cinchonine and quinine in solution with hydrochloric or sulphuric acid change more slowly at 36° C. than at 98° to 102° C. and the change at the latter temperature is very slight in 48 hours. With acetic or propionic acid the change is much more rapid, particularly if heated. Much of his work was done with the product formed by heating quinine with acetic acid. He was chiefly concerned in isolating and identifying quinotoxin and cinchotoxin. He bases his statements about toxicity on Hildebrandt's work.

Hildebrandt (*Arch. Exp. Path. and Pharmacol.*, 59, 127, 1908) produced his cinchotoxin by the action of acetic acid on cinchonine. This he administered to white mice. He says that 0.5 cc. of a 0.3 per cent. solution given to mice weighing 13 grams will produce severe cramps from which they recover, but die in a few days. This dose is equivalent to 0.00011 Gm. per gram body weight. Later on he says that the toxic dose is 0.00015 per gram body weight. The article does not state whether the weight of substance given is pure cinchotoxin or the product resulting from heating cinchonine with acetic acid. According to this worker quinotoxin is not as toxic as cinchotoxin.

Still earlier, in 1895, Miller and Rhode (*Ber. der Deutsche Chem. Ges.* XXVIII, 1058) worked with these products and named them cinchotoxin and quinotoxin, claiming that they are extraordinarily poisonous and the alkaloids lose their antipyretic effect.

Doctor Reid Hunt (*Arch. Inıernat. de Pharmacol.*, XII, 105, 1904) gave to a cat weighing 800 grams, by subcutaneous injection, 5 cc. of a 0.3 per cent. solution of cinchotoxin which caused severe cramps and death in a few minutes. The same sized dose of cinchonine produced only vomiting and recovery followed.

The work here recorded was not for the purpose of determining the presence of quinotoxin, but for the purpose of determining whether the mixture of quinine and aspirin, after standing sufficiently long to mass and become brown-red, is any more toxic than the mixture when first made. The results obtained are not conclusive, but on the whole are fairly satisfactory as far as they go.

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* Scientific Section, A. Ph. A., Buffalo meeting, 1924.

Incidentally it is interesting to note the length of time required for mixtures to change to a dark, clear, brown-red, viscid mass under different conditions. Biddle states that the formation of quinotoxin may be judged by the dark discoloration. Miller and Rhode also refer to this brown-red mass as being the toxic mixture.

The powder first begins to stick together, then cake and become hard. Contraction commences and goes on until the mass occupies one-half to one-third of the original volume. About the same time the color becomes dirty white, a dirty yellow, yellow, yellow-brown and brown-red. In contracting, the mixture recedes from the sides of the bottle, leaving an upright cylinder. This gradually softens and becomes a partially translucent, granular mass, which settles down and changes to a clear brown-red viscid mass.

Mixtures were made of aspirin with each one of the following—quinine sulphate, quinine bisulphate, quinine hydrochloride, quinine alkaloid, quinidine sulphate, quinidine alkaloid, cinchonine sulphate, cinchonine alkaloid, cinchonidine sulphate and cinchonidine alkaloid.

In each combination the aspirin was mixed with the crystallized alkaloidal compound; with the crystallized alkaloidal compound and citric acid; and with the dried alkaloidal compound, the loss in drying of which was made up by the addition of starch. Then portions of these were kept in corked bottles in the light, in corked bottles in the dark, in open bottles in the dark, in capsules in open bottles in the dark and in capsules in corked bottles in the dark. These samples have now been under observation for six months. The mixtures were made of equal weights of alkaloidal compound and aspirin and in those samples where citric acid was added, one-fifth as much acid as mixture was used. The samples of the dried alkaloidal compound in which the loss in weight was made up by the addition of starch gave practically the same results as where the crystalline alkaloidal substance was used or slightly less. The addition of citric acid increased the reaction in some cases and in others had practically no effect.

QUININE SULPHATE WITH ASPIRIN.

The mixture of crystallized quinine sulphate with aspirin caked slightly in six months, but the cake could be easily broken to a powder. Keeping in the different conditions enumerated above seemed to cause no difference in the appearance. The samples in which the sulphate had been dried were all in a good powdered condition at the end of six months. The mixtures containing citric acid had all caked, and contracted and assumed a dirty yellowish color; the samples in open bottles had changed most and the samples exposed to light came next. An old sample of two grains of crystallized sulphate with 3 grains of aspirin which had been kept for one and a half years had caked and contracted some, but had not begun to liquefy.

QUININE BISULPHATE WITH ASPIRIN.

All of the samples of aspirin with quinine bisulphate, crystallized, dried, or mixed with citric acid, kept under the conditions named above, changed but little in six months. The sample mixed with citric acid and kept in the light had turned to a yellowish color and caked some so that it would not jar to a complete powder. The other samples were not discolored or caked. An old mixture of two grains of quinine bisulphate and three grains of aspirin, which had been kept for a year and a half, had caked and become slightly discolored, but had not begun to contract.

QUININE ALKALOID AND QUININE HYDROCHLORIDE WITH ASPIRIN.

The mixture of quinine alkaloid and aspirin, exposed to the light, had changed to a dark brown opaque mass in four months and to a brown-red, transparent viscid mass in six months. A similar sample kept in the dark had not changed quite as much. Samples exposed to air, but kept in the dark, changed still less.

Samples of quinine hydrochloride, crystallized, dried, or mixed with citric acid, exposed to the various conditions, in general resembled the quinine sulphate sample, but had changed a little more.

QUINIDINE ALKALOID AND QUINIDINE SULPHATE WITH ASPIRIN.

Samples of quinidine sulphate, exposed to the various conditions, had in general changed considerably more than the quinine sulphate samples. In fact, the samples of the crystallized salt with aspirin, exposed to the light, was partly liquefied.

Samples of quinidine alkaloid with aspirin did not change as much as quinine alkaloid with aspirin. Those exposed to air massed and became yellow, occupying about one-third of the original volume. Samples in corked containers caked a little, but not to the point of shrinking.

Samples of cinchonine sulphate with aspirin and of cinchonine alkaloid with aspirin were very similar to the corresponding mixtures of quinine sulphate and quinine alkaloid. Samples containing cinchonidine sulphate with aspirin were similar to the corresponding quinine mixtures, but those containing cinchonidine alkaloid with aspirin had not changed as much as the corresponding quinine mixtures.

For testing the toxicity of the quinine-aspirin mixture the animal chosen was the frog because it is easily obtained, easily handled and quite susceptible. The solution was injected into the lymph sac underneath the tongue and the time noted before death.

Before attempting any experiments with the mixture of quinine and aspirin which had changed to a soft sticky mass of a dark reddish color, it was necessary to determine the toxicity of quinine alone, of aspirin alone, of a fresh mixture of quinine and aspirin, and also the available solvents. The question of solvent was an important one. Water does not dissolve aspirin readily, but still sufficiently so that it could be used and it could also be used for quinine bisulphate, but it would not dissolve the product formed by the reaction of quinine and aspirin on standing. Alcohol will dissolve all three, but the solution of the supposed toxic mixture cannot be diluted much with water without giving a heavy precipitate, and strong alcohol itself is quite fatal in quantities over 0.01 cc. per gram body weight as seen in Table I.

TABLE I.—EFFECT OF ALCOHOL.

Frog number.	Wt. in Gm. of frog.	Cc. given.	Cc. per Gm. body weight.	Results.
32	37	0.9	0.025	Dead in 1 hour
65	38	0.76	0.02	Dead in 1 hour
66	44	0.44	0.01	Alive after 24 hours

Ethylene Glycol.—It was found that ethylene glycol is a good solvent for aspirin, for quinine and its salts, and for the old quinine-aspirin mixture. A solution of each of these can be diluted with one-third of its volume with water without precipitation. It is less toxic than alcohol, as shown in Table II.

TABLE II.—EFFECT OF ETHYLENE GLYCOL.

Frog number.	Wt. in Gm. of Frog.	Cc. given.	Cc. per Gm. body weight.	Results.
30	40	1.0	0.025	Alive after 24 hours
33	28	0.56	0.02	Alive after 24 hours
63	44	1.32	0.03	Alive after 24 hours
64	47	1.9	0.04	Alive after 24 hours
84	25	1.00	0.04	Dead in 3 hours
85	24	1.2	0.05	Dead in 3 hours

The minimum toxic dose of ethylene glycol is approximately 0.04 cc.

Water.—To see if the injection of a reasonable amount of water would prove deleterious, 0.06 and 0.08 cc. per gram body weight were injected into two frogs without apparent ill effect.

Aspirin.—To determine the toxic dose of aspirin, a one per cent. solution of aspirin in a one per cent. solution of sodium citrate, a two per cent. solution in a two per cent. solution of sodium citrate, and a two per cent. solution in a mixture of three parts of ethylene glycol and one part of water were used as shown in Table III.

TABLE III.—EFFECT OF ASPIRIN.

Frog number.	Wt. in Gm. of frog.	Cc. given.	Gm. aspirin per Gm. body weight of frog.	Results.
11	32	0.32 (*a*)	0.0001	Alive after 24 hours
12	27	0.54 (*a*)	0.0002	Alive after 24 hours
24	33	0.50 (*b*)	0.0003	Alive after 24 hours
31	48	0.72 (*c*)	0.0003	Alive after 24 hours
27	27.5	0.48 (*b*)	0.00035	Alive after 24 hours
88	23	0.36 (*c*)	0.00035	Alive after 24 hours
22	22	0.44 (*b*)	0.0004	Dead in 1 hour
34	32	0.64 (*c*)	0.0004	Dead in 1 hour
86	31	0.62 (*c*)	0.0004	Dead in 20 hours
23	23	0.96 (*b*)	0.0008	Dead in 30 minutes

(*a*) 1% solution in 1% solution sodium citrate.
(*b*) 2% solution in 4% solution sodium citrate.
(*c*) 2% solution in 2% solution of 75% ethylene glycol.

The minimum toxic dose of aspirin is close to 0.0004 Gm. per gram body weight of the frog.

Quinine.—In testing the toxicity of quinine, the bisulphate was used because of its solubility in water. It was given dissolved in water and also dissolved in a mixture of ethylene glycol three parts and water one part, as shown in Table IV.

TABLE IV.—EFFECT OF QUININE BISULPHATE.

[Frog number.	Wt. in Gm. of frog.	Cc. given.	Gm. quin. bi-sulph. per Gm. body weight of frog.	Results.
5	34.5	0.18 (*a*)	0.00005	Alive after 24 hours
7	39.5	0.32 (*a*)	0.00008	Alive after 24 hours
6	39	0.35 (*a*)	0.00009	Alive after 24 hours
8	32	0.32 (*a*)	0.0001	Alive after 24 hours
74	31	0.31 (*c*)	0.0001	Alive after 24 hours
4	33	0.33 (*a*)	0.0001	Dead in 1 hour
18	28	0.42 (*a*)	0.00015	Alive after 24 hours
35	45	0.34 (*b*)	0.00015	Alive after 24 hours
10	35	0.53 (*a*)	0.00015	Dead in 12 hours
72	37	0.56 (*b*)	0.00015	Dead in 2 hours
26	33	0.53 (*a*)	0.00016	Dead in $^1/_2$ hour

87	30	0.51 (*c*)	0.00017	Dead in 20 hours
44	33	0.32 (*b*)	0.00019	Dead in 1/2 hour
9	33	0.66 (*a*)	0.0002	Dead in 1/2 hour
19	27	0.54 (*a*)	0.0002	Dead in 40 min.
36	43	0.43 (*b*)	0.0002	Dead in 1 hour

(*a*) 1% solution of quinine bisulphate in water.
(*b*) 2% solution of quinine bisulphate in 75% ethylene glycol.
(*c*) 1% solution of quinine bisulphate in 75% ethylene glycol.

These results indicate that 0.00015 Gm. of quinine bisulphate per gram body weight of the frog is the minimum toxic dose. 0.00015 Gm. of quinine bisulphate is equivalent to 0.000104 Gm. quinine alkaloid.

FRESHLY MADE QUININE-ASPIRIN MIXTURE.

A fresh mixture of two parts of quinine alkaloid with three parts of aspirin was prepared. Of this a one per cent. solution in a mixture of ethylene glycol three parts and water one part was made. The effect of the injection is shown in Table V.

TABLE V.—EFFECT OF FRESH QUININE ALKALOID-ASPIRIN MIXTURE.

Frog number.	Wt. in Gm. of frog.	Cc. given.	Gm. of mixture per Gm. body weight of frog.	Results.
88	20	0.3	0.00015	Alive after 24 hours
93	29	0.435	0.00015	Alive after 24 hours
92	28	0.45	0.00016	Alive after 24 hours
94	38	0.608	0.00016	Alive after 24 hours
91	26	0.45	0.00017	Dead in 1 1/2 hours
95	29	0.493	0.00017	Dead in 1 1/2 hours
89	23	0.42	0.00018	Dead in 1 1/2 hours
90	19	0.38	0.0002	Dead in 1/2 hour

The minimum fatal dose of the mixture is approximately 0.00017 which is equivalent to 0.000068 Gm. of quinine alkaloid.

The first experiments were made with a mixture of 2 Gm. quinine bisulphate with 3 Gm. of aspirin, using a 2 per cent. solution in 1 part of water with 3 parts of ethylene glycol. The results are shown in Table VI.

TABLE VI.—FRESH QUININE BISULPHATE-ASPIRIN MIXTURE.

Frog number.	Wt. in Gm. of frog.	Cc. given.	Gm. mixt. per Gm. body weight.	Results.
39	47	0.24	0.0001	Alive after 24 hours
38	50	0.5	0.0002	Alive after 24 hours
69	35	0.35	0.0002	Alive after 24 hours
70	38	0.48	0.00025	Alive after 24 hours
78	35	0.46	0.00026	Dead in 2 hours
79	34	0.36	0.00027	Alive after 24 hours
80	28	0.4	0.00028	Dead in 2 hours
77	24	0.35	0.00029	Dead in 1 hour
37	39	0.59	0.0003	Dead in 45 min.

The fatal dose of this fresh mixture is about 0.00026 Gm. per Gm. body weight of frog. The weight of quinine bisulphate in this is 0.000104 Gm. which is equivalent to 0.0000717 Gm. of quinine alkaloid.

OLD QUININE-ASPIRIN MIXTURE.

The mixture of quinine and aspirin which was supposed to contain quinotoxin was made December 22, 1922, by mixing quinine alkaloid two grains with aspirin three grains. It had been kept in capsules in a rather loosely stoppered bottle.

At the time of using it was a soft sticky mass of a dark brown-red color and had quite a strong acetic odor. A one per cent. solution of this mixture in glycol-water solution was used. The results are shown in Table VII.

TABLE VII.—OLD QUININE ALKALOID-ASPIRIN MIXTURE.

Frog number.	Wt. in Gm. of frog.	Cc. given.	Gm. mixt. per Gm. body weight.	Results.
41	35	0.35	0.0001	Alive after 24 hours
68	30	0.3	0.0001	Alive after 24 hours
67	27	0.41	0.00015	Alive after 24 hours
52	39	0.59	0.00015	Dead in 1 hour
46	36	0.55	0.00016	Dead in 3 hours
50	41	0.66	0.00016	Dead in 1 hour
73	31	0.53	0.00017	Alive after 24 hours
48	33	0.56	0.00017	Dead in 3 hours
75	33	0.6	0.00018	Dead in 1 hour
42	44	0.84	0.00019	Dead in 6 hours
76	30	0.57	0.00019	Dead in 1 hour
40	37	0.74	0.0002	Dead in 1 hour
71	35	0.7	0.0002	Dead in 1 hour

The toxic dose of the old quinine-aspirin mixture is approximately 0.00016 Gm. Forty per cent. of the original mixture was quinine alkaloid. Forty per cent. of 0.00016 is 0.000064, corresponding to the quinine in the original mixture.

From the foregoing we see that the approximate minimum fatal dose per gram body weight of the frog is for

Aspirin	0.0004 Gm.	Fresh Quinine Bisulphate-Aspirin Mixture or its equivalent in Quinine Alkaloid	0.000104
Quinine Bisulphate or its equivalent in Quinine Alkaloid	0.000104	Old Quinine Alkaloid-Aspirin Mixture or its equivalent in Quinine Alkaloid	0.0000701
Fresh Quinine Alkaloid-Aspirin Mixture or its equivalent in Quinine Alkaloid	0.00017		0.00016
	0.000068		0.000064

Comparing the doses of quinine alkaloid represented in the last three mixtures, we find them running very close to one another, 0.000068, 0.0000701, 0.000064.

Comparing the doses of the fresh quinine alkaloid-aspirin mixture and the old mixture, 0.00017 and 0.00016, we find that they come remarkably close and we are forced to the conclusion that the old mixture has practically the identical toxicity as the fresh mixture. As the dose of the quinine alkaloid equivalent of the quinine bisulphate given is a little larger than the quinine alkaloid equivalent in the mixtures, it is probably that aspirin increases the toxicity of quinine to some extent.

SUMMARY.

I. Mixtures of aspirin with quinine sulphate or quinine bisulphate do not change much in appearance in six months.

II. A mixture of aspirin with quinine alkaloid will change much more quickly than with the sulphate.

III. Aspirin seems to increase the toxicity of quinine a little.

IV. The old mixture of quinine and aspirin which has changed to a brown-red mass is no more toxic than the fresh mixture.

ABSTRACT OF DISCUSSION.

A. H. Clark inquired relative to the toxicity of aspirin in mixture with quinine and regard-

ing relative toxicity of old and freshly prepared quinine and aspirin mixture. The author replied that there is very little difference in the toxicity.

I. M. Kolthoff asked whether the color of the mixture changed more rapidly in the light than when kept in a dark place and whether a chemical change took place when the color darkened.

To the first question he replied that there seemed to be a variance and to the other that he did not go into the chemical examination of the mixture. In answer to a question by J. C. Munch, he replied that about one hundred frogs had been used in the experimentation, and at room temperature.

W. H. Zeigler said that clinically mixtures of quinine and aspirin had been found toxic, *i. e.*, reported so by physicians. He asked Dr. Ruddiman if he intended to continue the work and if so he hoped that warm-blooded animals would be used. The author replied that this was his intention. In his opinion the toxic symptoms induced by the mixture were due to the idiosyncrasy of persons to that mixture—there are persons who have an idiosyncrasy for quinine.

Various questions were asked relative to methods employed in mixing; to all of these the author replied and results are shown in the paper. Chairman Snyder hoped that experimentation with mixture on warm-blooded animals would be presented in a paper by the author next year, so that the question of toxicity of this mixture, which has been discussed for a number of years, may be settled.

MODIFICATION OF COW'S MILK FOR INFANT FEEDING.*

BY ELIZABETH GATES AND WYLY M. BILLING.

There will be no dispute of the statement that the best food for normal infants is human milk. This is an axiom with the medical profession. But in many cases human milk is not available, and the physician must do what he can with cow's milk, a food perfect for the calf, but very imperfectly adapted to the infant. Its chief disadvantages are (1) the difference in ratio of fats, carbohydrates and proteins from human milk, (2) its greater acidity, and (3) its tendency to form large indigestible curds in the stomach.

The percentage composition of human and cow's milk as taken from Thorpe[1] is as follows:

	Water.	Fat.	Sugar.	Casein.	Albumen.	Ash.
Cow's milk	87.25	3.75	4.75	3.00	0.40	0.75
Human milk	88.20	3.30	6.80	1.00	0.50	0.20

The most serious difference lies in the percentage of casein, which is the most difficult of the ingredients to digest. This difference is usually overcome by diluting the milk, the dilution varying with the age of the infant. The amount of sugar in cow's milk is low, so it is always necessary to add sugar, and even more necessary if the milk is diluted. If the fat percentage falls too low, it can be brought up by the addition of cream. Although the ash content of cow's milk is so much higher than that of human milk, there is some difference in the relative amounts of salts present. The following comparison, taken from Hess,[2] shows the difference in 100 parts of ash:

	K_2O.	Na_2O.	CaO.	MgO.	F_2O_3.	P_2O_5.	Cl.
Human milk	30.1	13.7	13.5	1.7	0.17	12.7	21.8
Cow's milk	22.14	15.9	20.05	2.63	0.04	24.7	21.27

According to this table, it can be seen that on dilution it is possible to reduce the amounts of potassium and sodium in cow's milk below that of human milk, and since these salts are very necessary, it would seem best, at least for diluted milk, to

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* Scientific Section, A. Ph. A., Buffalo meeting, 1924.