threshold, or stronger, were mixed with strychnine in any form, marked nausea was noted by one of us. This was observed even though the solution was almost tasteless from neutralization of the sweet and bitter tastes. When strychnine in any form was mixed with solutions of saccharin or of dulcin at concentrations fifty times their sweetness threshold or above, a peculiar metallic flavor resembling dental amalgam was observed.

Variation of individuals in speed of bitterness perception was again confirmed. One of us was able to identify the bitter taste of strychnine at a given concentration in two to ten seconds, another required fifteen to twenty seconds. The opposite condition prevailed for detecting sweet tastes, the "bitter-slow" being "sweet-fast." These differences in rate of apperception were not associated with any marked variation in absolute threshold taste limen, which is in accord with our previous findings (2).

CONCLUSIONS.

1. Sucrose, saccharin and dulcin mask the bitter taste of strychnine as the alkaloid, sulphate or hydrochloride.

2. Sucrose masks the bitterness of the alkaloid and the salts to about the same extent, a concentration one hundred times its sweetness threshold masking fourteen to eighteen times the strychnine threshold.

3. A solution of saccharin one hundred times its threshold masks somewhat more than two times the threshold of the alkaloid, and five to seven times the thresholds of the salts.

4. A solution of dulcin twenty times its threshold masks somewhat less than two times the threshold of strychnine alkaloid, and somewhat more than three times the thresholds of the salts.

5. Increasing concentrations of sweetening agents increased their masking effects.

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PHARMACOLOGICAL AND CHEMICAL STUDIES OF THE DIGITALIS GROUP. I. ADONIS, APOCYNUM AND CONVALLARIA.*

BY JAMES C. MUNCH[1] AND JOHN C. KRANTZ, JR.[2]

Although a very large number of papers have been published dealing with various phases of studies conducted upon digitalis, no systematized and concerted investigation of the pharmacology and chemistry of other members of the digitalis

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group has been found in the literature. In this investigation, studies were collaboratively conducted upon adonis, apocynum and convallaria. The control products used for these studies were prepared from crude drugs identified by competent pharmacognosists. The bioassay records of two drug manufacturers over a period of some twenty years have been consulted to ascertain the variations in potency of these crude drugs, as offered in commerce. It should be appreciated that these examinations were made voluntarily, before the bioassay requirements of the U. S. P. or N. F. were made effective. In some instances tests were made upon the crude drug only: other samples were reassayed from time to time, to obtain some information on rates of deterioration. Samples of the finished products marketed as tinctures or fluidextracts by various manufacturers were collected and tested. Since no official standards have been prescribed for these products, it was thought of interest to determine the variation in potency of marketed products. It appears that at least some of the drug manufacturers have been voluntarily assaying and standardizing these preparations, even in the absence of official potency requirements. In addition, a detailed search of the literature has been made to learn the potency of such products as reported, even though the authenticity of the test product is not known. In this communication, our results are presented upon adonis, apocynum and convallaria, and certain active principles obtained from these drugs.

Clinical reports state that adonis, apocynum and convallaria resemble digitalis in many particulars in their effects upon the heart. Prescription surveys show that prescriptions are still being written for these products, although their use in the United States is much smaller than is the use of digitalis. Adonis has obtained a definite vogue in Russia, not only as a drug for exerting certain effects upon the heart, but also as a diuretic (4, 5, 9, 10, 15, 16, 17, 18, 22, 25, 29, 30, 32). A glucoside, adonidin, was extracted from adonis and clinical reports have suggested its value. Mercier and Mercier (25), in a detailed study of adonis, separated two glucosides, (1) adonidoside, which is water soluble, and (2) adonivernoside, which is insoluble in water, but soluble in chloroform. Adonidoside was found to be more cardiotropic and myotropic, having only a feeble action on the central nervous system; adonivernoside was a marked diuretic.

Over a hundred years ago it was reported that apocynum was an emetic, cathartic, diaphoretic and diuretic. Pharmacological and clinical studies showed that it had a specific effect upon the heart, resembling that of digitalis and that a glucoside, cymarin, extracted from apocynum had a similar activity. Because of its action as a diuretic, it has been called the "vegetable trocar" (30, 32). Some information in the literature suggested that there were differences in the activity of different species of apocynum. We have made tests on a number of samples of *Apocynum cannabinum* and of *Apocynum androsæmifolium* which were identified, root by root, by Professor William J. Stoneback for us. We found that fluidextracts prepared from each species showed precisely the same physiological activity. If cymarin is the active principle, as has been suggested, this would be expected in view of Cushny's report (5) that cymarin is identical whether extracted from *A. cannabinum*, *A. androsæmifolium* and *A. venetum*.

Studies on convallaria have shown that the flowers are richer in active principles than are the roots. Karrer (21) in a series of chemical studies supplementing

the earlier investigations of convallaria, (11, 16, 18, 20, 23, 24, 35) has obtained a crystalline glucoside, convallatoxin, which is somewhat less than twice as toxic for frogs as is ouabain.

Review of the literature on adonis showed that tests have been made upon frogs, guinea pigs, rabbits and cats; in Table I results reported in the original articles have been recalculated in terms of milligrams of crude drug or of active principle per kilo of body weight of animal. This permits immediate comparison of the potency of any extractive in terms of the crude drug. The bioassays which we have made are recorded in Table II. Studies of deterioration have been rather limited: results obtained in our one-hour frog study and in the study by the cat method reported in the literature are given in Table III. The chemical assay of the sample of fluidextract of adonis tested by the one-hour frog method in Table III was made by a modification of the Knudson-Dresbach method (1, 26). It was found chemically to be 104 per cent of the (chemical) potency of a standard digitalis product simultaneously assayed by the one-hour frog method and found to be in harmony with the U. S. P. X potency requirement. This result is in good agreement with that obtained by the one-hour frog method which showed the product to be 600/550, or 109 per cent of the requirement of the U. S. P. X for digitalis. It is suggested that, if adonis and its preparations are recognized in the forthcoming revision of the National Formulary, the one-hour frog method should be recommended for bioassay, and that the same potency requirement be established for adonis and its preparations as for digitalis and the corresponding digitalis preparations. In other words, adonis, by bioassay, has the same activity as digitalis.

Physiological potencies of apocynum preparations found in the literature are recalculated in terms of milligrams per kilo and given in Table IV. Holste (18) found by perfusion of the isolated frog heart that 0.24 mg. of cymarin was equivalent to 1 mg. of ouabain: other reports in the literature, using the same technique (26) give values of 0.85, 3.54 and 5.38 mg. of cymarin as equivalent to 1 mg. of ouabain. The purity of the cymarin used is unknown. In testing tincture of apocynum by the pigeon emesis method, Hanzlik (13) found that a dose equivalent to 9 mg. of crude drug per kilo produced emesis and 20 mg. per kilo produced death. Baljet's studies (1) by the Gottlieb thirty-minute frog method (26) showed that the M. S. D. of cymarin was 0.12 mg. per kilo, and of ouabain 0.03 mg. per kilo. Two fluidextracts of apocynum were assayed simultaneously by the one-hour frog and the M. L. D. cat method. For Sample A, the M. S. D. was 320 mg. per kilo, the M. L. D. cat value 55 mg. per kilo. For Sample B, the M. S. D. frog value was 280 mg. per kilo, the M. L. D. cat value, 23 mg. per kilo. Our results in assaying fluidextract of apocynum by the frog and guinea pig methods are given in Table V. The fluidextracts to which letters were arbitrarily signed are products purchased on the open market, and these fluidextracts A and B are not those just referred to. Three fluidextracts were reassayed by the frog and guinea pig methods from time to time over 172 weeks to follow any deterioration. One sample by both methods of assay showed an apparent increase in potency, but reassays were not made on these samples subsequently to learn whether these changes were apparent or real. The loss by the guinea pig method appeared to be greater than by the one-hour frog method which showed comparatively little change. The chemical assay showed this fluidextract to be 111 per cent of the potency of a similar digitalis

product, although the bioassays showed this product to be approximately twice the potency of the digitalis product. It is suggested that, if apocynum and its preparations are recognized in the forthcoming revision in the National Formulary no difference be made between various species, and that the one-hour frog method should be recommended for bioassay, and that the potency requirement established for apocynum and its preparations require them to have twice the strength of digitalis and the corresponding digitalis preparations. In other words, apocynum, by bioassay, should have twice the activity of digitalis.

Reports in the literature regarding the physiological potency of convallaria preparations are given in Table VII. Our studies on fluidextracts, are given in Table VIII and on deterioration in Table IX. The four samples studied by the one-hour frog method showed comparatively little deterioration over a period up to 153 weeks. Chemical assays of a fluidextract which was somewhat more than 300 per cent of the U. S. P. requirement for digitalis by the one-hour frog method showed only 70 per cent of the estimated potency. It is suggested that, if convallaria and its preparations are recognized in the forthcoming edition of the National Formulary, the one-hour frog method should be recommended for bioassay and the convallaria products should be three times as potent as the corresponding digitalis preparations. In other words, convallaria, by bioassay, should be three times as powerful as digitalis.

For ready reference, results of the bioassay and chemical assay, as well as the p_H of samples tested by the Wilson hydrogen electrode method are given in Table X.

TABLES.

TABLE I.—REPORTED PHYSIOLOGICAL POTENCY OF ADONIS PREPARATIONS.

All data recalculated to mg./Kg.

		Method of Assay.				
		Frog.		Guinea Pig	Rabbit	Cat
Ref.	Product.	M. S. D. 1 Hr.	M. L. D.	M. L. D. Subcu.	M. L. D. I. V.	M. L. D. I. V.
8	Fluidextract	400	....	..	..	...
17	Fluidextract	450	....	..	..	...
29	Fluidextract	360–430	....	600	..	...
2	Fluidextract	460	3600	..	..	...
31	Fluidextract	450	....	..	..	...
7	Fluidextract	...	....	..	..	100
15	Fluidextract	...	....	..	..	100–140
8	Adonidin	4	....	..	..	...
4	Adonidin	...	3	..	1	...
10	Adonidin	...	38	..	4.6	...
7	Adonidin	...	....	..	..	4.34
14	Adonidin	...	....	..	..	3.0
16	Adonidoside	...	3	..	2.5	...
9	Adonidoside	...	2.5	..	..	0.7
25	Adonidoside	...	2.5	3.5	1.0	...
22	Adonidoside	...	3.3	..	..	4.7
16	Adonivernoside	...	3.7	..	2.0	...
9	Adonivernoside	...	5.9	..	..	1.3
25	Adonivernoside	...	6.0	6.0	2.0	2.2
22	Adonivernoside	...	4.5	..	0.19	2.3

TABLE II.—BIOASSAYS OF ADONIS PREPARATIONS.

All data recalculated to mg./Kg.

Product.	Sample Number.	Frog M. S. D. 1 Hr.	Guinea Pig M. L. D. Subcu.
Crude drug	1	420	480
Fluidextract	2	625	800
Fluidextract	3	610	...
Adonidin	4	5	5.4

TABLE III.—DETERIORATION OF ADONIS PREPARATIONS.

All data recalculated to mg./Kg.

Assay Method.	Original Potency.	Reassay. Age Wks.	Potency.	Loss in Activity Per Cent.
M. S. D. 1-hr. frog	420	166	550	24
M. L. D. Cat*	57	36	88	35
M. L. D. Cat*	188	36	262	28

* Product stored was tincture in 70 per cent alcohol (15).

TABLE IV.—REPORTED PHYSIOLOGICAL POTENCY OF APOCYNUM PREPARATIONS.

All data recalculated to mg./Kg.

Ref.	Product.	Method of Assay. Frog. M. S. D. 1 Hr.	Frog. M. L. D.	Guinea Pig M. L. D. Subcu.	Rabbit M. L. D. I. V.	Cat M. L. D. I. V.
8	Fluidextract	120	..	...	...	....
27	Fluidextract	...	..	240	..	....
12	Fluidextract	...	..	300	...	....
7	Fluidextract	...	..	...	...	66
13	Fluidextract	...	..	...	...	70
20	Cymarin	...	..	...	...	0.1
26	Cymarin	...	0.7	...	...	0.125
32	Cymarin	...	0.8*	...	...	....
			2.0[1]			
21	Cymarin	...	0.67	...	...	....

* *Rana temporaria.*

[1] *Rana esculenta.*

TABLE V.—BIOASSAYS OF APOCYNUM PREPRATIONS.

All data recalculated to mg./Kg.

Product.	Sample Number.	Frog M. S. D. 1 hr.	Guinea Pig M. L. D. Subcu.
Fluidextract	1	320	...
Fluidextract	2	280	...
Fluidextract	3	...	160
Fluidextract	4	...	220
Fluidextract	3	...	240
Fluidextract	6	...	400
Fluidextract	7	...	340
Fluidextract	8	320	...
Fluidextract	9	390	...
Fluidextract	10	...	260
Fluidextract	11	250	180
Fluidextract	12	250	180

Fluidextract	13	280	250
Fluidextract	14	220	200
Fluidextract	15	...	250
Fluidextract	A	...	240
Fluidextract	B	...	320
Fluidextract	C	280	180
Fluidextract	D	250	200
Fluidextract	E	280	190

TABLE VI.—DETERIORATION OF APOCYNUM PREPARATIONS.

All data recalculated to mg./Kg.

		Reassay.		
Assay Method.	Original Potency.	Age Weeks.	Potency.	Loss in Activity Per Cent.
1-hour frog	250	156	280	11
		172	260	4
1-hour frog	280	16	220	(27)
1-hour frog	220	16	230	4
M. L. D. Guinea Pig	160	76	480	67
M. L. D. Guinea Pig	220	4	180	(22)
M. L. D. Guinea Pig	240	106	400	40
		108	430	30

TABLE VII.—REPORTED PHYSIOLOGICAL POTENCY OF CONVALLARIA PREPARATIONS.

All data recalculated to mg./Kg.

		Method of Assay.				
		Frog.		Guinea Pig	Rabbit	Cat
Ref.	Product.	M. S. D. 1 Hr.	M. L. D.	M. L. D. Subcu.	M. L. D. I. V.	M. L. D. I. V.
11	F. E. Root	...	167	...	...	...
35	F. E. Root	...	200–250	...	...	...
28	F. E. Root	...	30*	60	...	...
			50–90[1]			
3	F. E. Root	...	40–70	...	30–70	...
19	F. E. Root	...	250	...	...	...
34	F. E. Root	...	210	...	...	...
8	F. E. Root	200	...	...	...	...
27	F. E. Root	...	...	300	...	...
12	F. E. Root	...	...	300	...	2–
26	F. E. Root	...	...	...	...	50
11	F. E. Herb	...	107	...	...	...
21	F. E. Herb	...	100	...	...	...
35	F. E. Herb	...	150–330	...	...	...
19	F. E. Herb	110–220	100–240	...	...	...
8	F. E. Herb	187	...	...	...	...
11	F. E. Flowers	...	80	...	...	...
11	F. E. Flowers (Freshly dried)	...	50	...	...	...
11	F. E. Flowers (5 yrs. old)	...	90	...	...	...
21	F. E. Flowers	...	55	...	...	...
35	F. E. Flowers	...	100	...	...	...
19	F. E. Flowers	...	90	...	...	...
8	F. E. Flowers	75	...	...	...	...

TABLE VII.—*Continued.*

21	Convallamarin	...	10	...	...	...
35	Convallamarin	...	15	...	...	...
23	Convallamarin	0.3–0.6	...	...	...	...
8	Convallamarin	4.5	...	...	...	...
6	Convallamarin	4.75	...	...	...	...
24	Convallamarin	...	...	...	3–4	...
7	Convallamarin	...	...	...	...	1.68
21	Convallatoxin	...	0.33	...	...	...

* *Rana temporaria.*

[1] *Rana esculenta.*

TABLE VIII.—BIOASSAYS OF CONVALLARIA PREPARATIONS.

All data recalculated to mg./Kg.

Product.	Sample Number.	Frog. M. S. D. 1 Hr.	Guinea Pig M. L. D. Subcu.
Fluidextract	1	...	140
Fluidextract	2	220	...
Fluidextract	3	200	...
Fluidextract	4	200	...
Fluidextract	5	...	300
Fluidextract	6	...	280
Fluidextract	7	...	300
Fluidextract	8	...	320
Fluidextract	9	...	240
Fluidextract	10	...	120
Fluidextract	11	...	160
Fluidextract	12	110	...
Fluidextract	13	150	...
Fluidextract	14	...	180
Fluidextract	15	180	...
Fluidextract	16	150	100
Fluidextract	17	140	100
Fluidextract	18	180	80
Fluidextract	19	170	...
Fluidextract	20	250	260
Fluidextract	21	200	120
Fluidextract	22	195	...
Fluidextract	A	167	160
Fluidextract	B	125	80

TABLE IX.—DETERIORATION OF CONVALLARIA PREPARATIONS.

All data recalculated to mg./Kg.

Assay Method.	Original Potency.	Reassay. Age Wks.	Reassay. Potency.	Loss in Activity Per Cent.
1-hour frog	175	136	190	9
		152	180	3
1-hour frog	180	1	175	(3)
		137	175	(3)
		153	220	18
1-hour frog	170	28	200	15
		36	200	15
1-hour frog	200	72	170	(18)
		100	200	0
		116	220	9

TABLE X.—COMPARISON OF PHARMACOLOGICAL AND CHEMICAL ASSAYS.

Product.	Potency as Per Cent U. S. P. Tr. Digitalis. 1-Hour Frog.	Chemical.	p_H.
Standard Tr. Digitalis	100	100	..
Tr. Adonis	109	104	5.99
Tr. Apocynum	230	111	5.13
Tr. Convallaria	300	70	5.96
Ouabain:			
53 gamma/cc.	65	81	..
82 gamma/cc.	100	125	..

CONCLUSIONS.

1. Adonis and its preparations bioassayed by the one-hour frog method should have the same potency as digitalis and the corresponding digitalis preparations.

2. Apocynum should have twice the potency of digitalis by the one-hour frog method of assay.

3. Convallaria should be three times as potent as digitalis by the one-hour frog method of assay.

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SOME CONSIDERATIONS OF SILVER PICRATE.*

BY JOHN C. BIRD AND ALFRED BAROL.

This presentation is intended to cover some of the outstanding points evolved during recent work with silver picrate, certain particular merits of which would seem to have hitherto been overlooked. It is hoped that some of the promising results reported here will act as a stimulus to further clinical investigation of this product.

A survey of the literature covering the last 100 years is disappointing in the scarcity of data concerning silver picrate. The compound was first produced as a by-product by Chevreul, in 1809, during his work on indigo and later by Liebig in 1828, who named it "silver carbazotate," and noted its explosive property. To Dumas (1) however, might be ascribed the credit of first preparing silver picrate, as such, from silver nitrate and ammonium picrate, in 1841. Dumas published an analysis of the compound and evidently stimulated further work, for both Lau-

* Scientific Section, A. PH. A., Washington meeting, 1934.