As these combinations cannot be analyzed chemically, you can readily see how highly essential it is that before this drug can be placed on the market its toxicity has to be determined by means of biological assays, using rabbits, guinea pigs or rats.

The arsenic content of the various Arsphenamine preparations on the market averages around thirty percent, which is the standard set by the Hygienic Laboratory of the United States Public Health Service, while the arsenic content in the Neo-derivative should average around nineteen percent.

The present biological standard set by the same Laboratory, for the Maximum Tolerated Dose, is 100 milligrammes per kilo-body-weight of animal for Arsphenamine; it is 200 milligrammes per kilo-body-weight for Neo-Arsphenamine.

The dose for Arsphenamine usually given to adults is from 0.4 to 0.6 gramme, while from 0.6–0.75 gramme is the usual dose for Neo-Arsphenamine.

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THE PERMANENCE OF ALKALOIDAL FLUIDEXTRACTS AND TINCTURES.*

(SECOND PAPER.)

BY WILBUR L. SCOVILLE.

Nine years ago, at the Richmond meeting, I reported, under the above title, upon the keeping qualities of some fifty alkaloidal fluidextracts and tinctures over a period of two to three years. The remaining portions of those preparations were set aside in a closed case having glass doors where they have been stored during the intervening time. The preparations are now ten to twelve or more years old, and have been stored during that period under conditions which simulate the ordinary storage of business, namely, in partially filled bottles, in a fairly even temperature, and in a diffused light. They were each assayed by the same method as used ten years ago, and the results are shown in the following table.

The column headed "standard" shows the strength (grammes per 100 mils) to which the preparations were adjusted by assay when made.

TABLE OF RESULTS.

Abbreviations in tabular matter: F.—fluidextract; T.—tincture. Under "physical condition," the extent and character of the precipitate are indicated as follows: Slight precipitate—s; very slight—v. s.; moderate—m.; dense—d.; heavy—h.; considerable—c.; gelatinous—g.; wholly gelatinized—w. g. For fluidextracts of cinchona, guarana, ipecac and kola see also statements indicated by key number to foot-notes. Abbreviated references to preparations without precipitates are: O—clear; N—nearly clear; A—acetic.—EDITOR.

Made.	Percent alcohol.	Preparation.	Standard.	Assay 1910.	Assay 1919.	Percent loss.	Physical condition.
7–'07	40	F. Aconite lf.....	0.40	0.50	0.44	00.0	s.
1–'08	65	F. Aconite rt.....	0.40	0.43	0.407	00.0	N
1–'07	63	T. Aconite rt.....	0.050	0.051	0.0486	3.0	s.
10–'07	75	F. Anhalonium.....	5.50	6.48	5.6	00.0	v.s.
7–'08	50	F. Aspidosperma.....	1.00	1.04	0.53	47.0	h.
3–'08	60	F. Belladonna lf.....	0.30	0.297	0.277	8.0	m.

* Read before Scientific Section, A. Ph. A., New York Meeting, 1919.

TABLE OF RESULTS.—(*Continued*).

Made.	Percent alcohol.	Preparation.	Standard.	Assay. 1910.	Assay. 1919.	Percent loss.	Physical condition.
9–'08	65	F. Belladonna rt.....	0.40	0.383	0.385	4.0	m.
2–'08	48	T. Belladonna lf.....	0.030	0.028	0.028	7.0	s.
5–'07	58	F. Cinchona Cal.....	4.00	2.85	2.20	44.0	c.[1]
8–'07	56	F. Cinchona Pale.....	3.00	2.72	2.56	15.0	m.
11–'07	56	F. Cinchona Red.....	5.00	4.75	4.60	8.0	s.
4–'08	53	F. Cinchona Comp.....	3.00	3.00	3.02	0.0	s.
2–'07	63	T. Cinchona Cal.....	0.75	0.63	0.56	25.0	h.
4–'08	64	T. Cinchona Comp.....	0.60	0.61	0.59	1.0	c.
8–'08	38	F. Coca.....	0.50	0.49	0.15	70.0	h.
5–'07	25	F. Coca misc.....	0.50	0.47	0.26	48.0	h.
12–'07	55	F. Colchicum corm.....	0.35	0.31	0.24	30.0	v. s.
3–'08	55	F. Colchicum seed.....	0.40	0.30	0.26	35.0	v. s.
2–'08	56	T. Colchicum seed.....	0.040	0.050	0.037	8.0	v. s.
8–'07	40	F. Conium.....	0.45	0.27	0.049	90.0	c.
12–'07	55	F. Gelsemium.....	0.50	0.42	0.49	2.0	O
5–'08	55	F. Gelsemium fresh.....	0.25	0.23	0.25	0.0	c.
3–'08	60	T. Gelsemium.....	0.05	0.041	0.038	24.0	s.
5–'08	60	F. Guarana.....	3.50	3.68	1.45	59.0	h[2].
8–'08	47	F. Hydrastis.....	2.00	2.06	1.86	7.0	s.
3–'08	60	T. Hydrastis.....	0.40	0.344	0.288	28.0	m.
12–'07	55	F. Hyoscyamus.....	0.075	0.073	0.0074	2.0	m. h.
6–'08	46	T. Hyoscyamus.....	0.0075	0.0072	0.0074	2.0	s.
10–'08	68	F. Ignatia.....	1.50	1.45	1.46	3.0	s.
2–'08	57	F. Ipecac Cart.....	1.75	1.78	1.39	20.0	g.[3]
1–'08	57	F. Ipecac Rio.....	1.75	1.70	1.40	20.0	g.[4]
	28	F. Kola N. F.....	1.00	0.92	0.93	7.0	c.
8–'08	52	F. Kola fresh.....	0.65	0.70	0.00	100.0	w. g.[5]
8–'08	60	F. Nux Vomica.....	1.00	0.976	1.002	0.0	v. s.
6–'08	68	T. Nux Vomica.....	0.10	0.098	0.100	0.0	v. s.
6–'08	45	T. Opium.....	1.25	1.25	1.034	17.0	c.
4–'08	22	T. Opium deod.....	1.25	1.25	1.115	8.0	c.
11–'08	32	F. Opium Comp.....	4.82	4.58	4.06	16.0	m.
11–'07	88	F. Physostigma.....	0.15	0.157	0.138	8.0	s.
5–'08	92	T. Physostigma.....	0.014	0.016	0.016	0.0	v. s.
6–'08	43	F. Pilocarpus.....	0.40	0.33	0.35	12.5	s.
3–'08	Acet	F. Sanguinaria A.....	2.50	0.57	0.17	96	c.
2–'09	60	F. Sanguinaria.....	2.50	1.63	0.56	78	h.
3–'08	56	T. Sanguinaria.....	0.25	0.092	0.090	64	c.
11–'06	68	F. Scopola.....	0.50	0.505	0.51	0.0	s.
8–'07	52	F. Stramonium lf.....	0.25	0.27	0.236	6.0	m.
3–'07	63	F. Stramonium seed.....	0.35	0.326	0.34	3.0	m.
2–'08	48	T. Stramonium.....	0.025	0.025	0.018	28.0	s.
1–'08	85	F. Veratrum.....	1.00	0.70	0.60	40	O
4–'08	93	T. Veratrum.....	0.10	0.070	0.062	38	O

A study of this table discloses that there are two main reasons for deterioration in these preparations: (1) the unstable character of some of the alkaloids, and (2) precipitation of secondary constituents by which alkaloids are taken out of the solution.

Loss through the instability of the alkaloid is shown particularly in the fluid-

[1] One and one-half inch precipitate. [2] 102 grammes moist precipitate. [3] 1/8 inch gelatinous precipitate. [4] 1/8 inch gelatinous precipitate. [5] Wholly gelatinous.

extracts of colchicum corm and colchicum seed. Both of these have lost more than a third of their strength, yet they remain nearly clear. The tincture shows much less loss, and contains a marked precipitate.

The fluidextract and tincture of veratrum show a loss of 40 percent, but are clear and, so far as physical appearance shows, are in excellent condition. Probably the deterioration in this is due entirely to partial decomposition of the alkaloids.

Sanguinaria shows the greatest loss of any of the preparations, the acetic fluidextract, which was formerly official, being almost inert. The sanguinaria alkaloids are easily changed, and in assaying the aged preparations it was evident from the appearance of the acid solutions that sanguinarine was present only in small amounts, if at all, since the blood-red color of acid solutions was lacking. The solution obtained from the acetic fluidextract had a yellow coloring in which no red was observed, while that from the alcoholic fluidextracts and tincture showed only a light orange color. This alone indicated a decomposition of the alkaloids, since in fresh preparations the color is a deep blood red, and the extraction of the alkaloid by acid can be closely followed by the color of the solutions. Precipitation is heavy in these preparations and may also be a factor in deterioration.

With coca and pilocarpus, decomposition of the alkaloid is doubtless the main factor in loss, but precipitation is also a secondary cause. Preparations of both of these precipitate badly.

It is especially noticeable, however, that the mydriatic alkaloids, which are generally regarded as unstable, show no serious losses on aging. Of all the preparations of belladonna, hyoscyamus, scopola and stramonium, the only one showing a loss of more than 8 percent is tincture of stramonium. Hyoscyamus preparations show only 2 percent loss, though previous reports by other invesigators have shown much greater losses.

Why the tincture of stramonium should undergo a deterioration of 28 percent is a puzzle. It shows less precipitate than some of the other stramonium and belladonna preparations, and it contains the same amount of alcohol as tincture of belladonna, which shows only 7 percent loss. Taken as a whole, the mydriatic preparations show an unexpected degree of stability.

Physostigma preparations are also stable to a surprising degree. Perhaps the alcoholic strength is a factor in this.

The aconite preparations also show no appreciable loss. Chemical assay in this instance is not conclusive, since the decomposition products of aconitine have a lower molecular weight and consequently show a higher titration value, and one is not certain in titration how much is aconitine and how much is aconine. But a comparison of the results by weight and by titration indicate that aconitine formed the greater portion of the alkaloid.

Among the preparations which show a loss in strength caused by the mechanical absorption of the alkaloids by the precipitate which is formed, those which contain tannoid bodies are conspicuous. Such are aspidosperma, cinchona, coca, kola, and guarana. The tannins in these drugs appear to oxidize easily and become insoluble, and in precipitating they carry down the alkaloids.

It is noticeable that in preparations of these drugs, loss in strength is appar-

ently proportional to the amount of precipitate. When there is no precipitate, there is no loss in strength, and when the precipitate is heavy the loss in the fluid is considerable.

That the precipitate carries down the alkaloid mechanically was shown in 1910 in the case of a fluidextract of cinchona which had dropped from 4 percent of ether-soluble alkaloids to 3.3 percent and which contained 75 grammes of moist precipitate containing 4.84 percent of ether-soluble alkaloids.

The case of fluidextract of guarana, which assayed 3.5 percent of caffeine in 1908 and 3.68 percent in 1910, when precipitation had begun, yielded only 1.45 percent in 1919; but it contained 102 grammes of dense, leather-like precipitate which could not be removed from the bottle without breaking the latter. This precipitate assayed 6.88 percent of caffeine. Apparently the first portions of precipitate did not occlude the alkaloid, but as it increased, alkaloid was absorbed from the liquid.

A similar case is shown in fluidextract of fresh kola, which showed only a slight precipitate in 1910 and tested 108 percent of standard, but had wholly gelatinized in 1919. Unfortunately this gelatinous mass was thrown away without assay.

Both samples of fluidextract of ipecac show a loss of 20 percent and contain considerable caked precipitate. Since ipecac does not contain tannin this precipitate is of a different character, but presumably it contains some of the alkaloids.

With opium the precipitate is of a resinous character, as shown by its partial solubility in 95 percent alcohol. It was found to contain morphine, but not in sufficient amount to account for the loss in the tinctures.

In general, the presence of a considerable quantity of precipitate in a fluidextract or tincture may be taken as an evidence of deterioration in strength. Evidently the precipitate does not consist of inert matter, as has frequently been taught, but contains more than its proportionate share of active principles, even when these are freely soluble in themenstruum. A slight or very moderate amount of precipitate does not necessarily indicate deterioration, as shown in the case of belladonna, hyoscyamus, and stramonium (fluidextract), but on the other hand even a clear fluid may have deteriorated, as shown by veratrum and colchicum preparations.

It is also interesting to note that tinctures show, in the cases of aconite, belladonna, and compound cinchona, slightly more, and in cinchona calisaya, gelsemium, hydrastis, and stramonium considerably more deterioration than the corresponding fluidextracts.

The influence of alcoholic strength is not so clear, from the table. With the exception of the opium, coca and kola preparations, all contained above 45 percent of alcohol. It is to be remembered that the tendency of late years has been to increase the strength of drug menstrua to prevent precipitation. This seems a wise tendency in so far as it effects this purpose, because not only the solubility of the alkaloids but the influence of other constituents of the drug, which may in themselves be inert, is important. The question of the strength of alcohol needed to extract the active principles and prevent fermentation changes, which is now being argued, is not sufficient if we are to have reliable preparations. The influence

of alcohol in excluding inert but instable constituents, in preventing oxidation, or in otherwise maintaining solution, is of prime importance. Stability and reliability in galenical and pharmaceutical preparations are of more importance than alcoholic restrictions.

As a whole, the preparations of our active potent drugs show a very satisfactory degree of stability during a considerable period.

LABORATORY OF
PARKE, DAVIS & COMPANY,
1919.

AN UNUSUAL METHOD FOR TESTING THE ALCOHOLIC STRENGTH OF PHARMACEUTICALS.*

BY WILLIAM G. TOPLIS.

On page 115 of the February 1919 issue of the *American Journal of Pharmacy* will be found a contribution by two Hindu gentlemen[1] connected with the Hindu University Chemical Laboratory at Benares, India, entitled, "A Simple and Rapid Method for the Estimation of Alcohol in Spirituous Liquors."

This is an example of widely separated minds operating along similar lines, each quite unknown to the other. The writer had occasion to visit Prof. C. H. LaWall some time before this article appeared in print, and one of the topics of discussion was this very subject.

The following is quoted from their paper to explain the method: "The method for the estimation of alcohol described below is the result of an investigation to devise a simple method for its estimation with a fair degree of accuracy, avoiding distillation."

The method consists of treating a known quantity of spirituous liquor, in a glass tube, graduated in tenths of a cubic centimeter, or finer, with an excess of anhydrous potassium carbonate, adding five to ten percent of water in case the alcohol is above ninety percent. The mixture is then thoroughly shaken and allowed to settle (or preferably centrifuged) when it will separate into a lower layer of solid potassium carbonate, a middle layer of solution (saturated) of potassium carbonate, and an upper layer of alcohol hydrate corresponding with the formula $4C_2H_5OH\text{-}H_2O$. The authors here set forth the evidence of the truth of their statements, and the method by which it was secured. They have treated the subject with great care and show that the method is dependable and gives precise results. To the purely chemical investigator thus far ends the chapter. To the pharmaceutical observer there appears a further usefulness. Employing a similar method with different agents it is possible to determine with useful accuracy, not alone the alcohol in a preparation but certain substances soluble in dilute alcohol that are insoluble in concentrated alcohol or saturated solution of a salt; for example, essence of pepsin or wine of pepsin may be made to disclose, in addition to the alcohol, the pepsin content as well, by placing a known quantity of either preparation in a test tube and simply saturating the liquid with potassium citrate (previously dried); immediately the alcoholic part will rise to form the

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* Read before Scientific Section, A. Ph. A., New York Meeting, 1919.

[1] Magendra Chandra Nag and Panna Lal.