A STUDY OF VEHICLES FOR MEDICINES.*

BY BERNARD FANTUS, H. A. DYNIEWICZ AND J. M. DYNIEWICZ.

1. THE ERIODICTYON PREPARATIONS.

Eriodictyon preparations are, at the present, chiefly used as disguising vehicles for bitter remedies, such as quinine; for which purpose they were first recommended by Rother (1) who believed that this disguising value depended upon the formation of insoluble quinine resin salts from which the quinine could be readily assimilated.

From an historic standpoint it is of interest that the Indians of California and Mexico employed this resinous evergreen plant, in the form of infusion or decoction in whisky, as a remedy for consumption, so that it came to be known as "Consumptives' Weed." The "electic" physician, J. H. Bundy (2), who in 1875 introduced eriodictyon to medical notice, also ascribed to it expectorant value in "chronic lung cases," though none in acute coughs and colds. The fact that no such use is made of this drug, at the present time, suggests that it has no particular value for these purposes: for a remedy whose clinical value can be definitely demonstrated is not likely to be abandoned.

As we were unable to discover, from a study of the literature, excepting for Rother's suggestion, as to what ingredient eriodictyon owed its disguising value, we proceeded to separate the known proximate principles of eriodictyon; and to study their quinine disguising action. Thus, we isolated eriodictyol and homo-eriodictyol, both of which were separated by us in pure crystalline form. Eriodictyol, of which the fluidextract yields about 0.23%, was obtained in the form of small, fawn-colored plates. It is soluble in hot alcohol and acetic acid, sparingly soluble in boiling water and most other organic solvents. Homo-eriodictyol is present in a larger amount (about 3%) and crystallized in glistening leaf-shaped masses possessing a silky luster. It is less soluble in water than eriodictyol and more readily soluble in alcohol and acetic acid. Both eriodictyol and homo-eriodictyol had no obvious effect in the disguising of quinine.

That the resins of eriodictyon constitute the "active principle," as far as disguising of quinine is concerned, has become evident to us from experiments, which will be presented in the following order: 1. Fluidextract of Eriodictyon and Quinine. 2. Fluidextract of Eriodictyon and Strychnine. 3. Fluidextract of Eriodictyon and Codeine. 4. Fluidextract of Eriodictyon and Methylene Blue. 5. Resinoid of Eriodictyon and Methylene Blue.

FLUIDEXTRACT OF ERIODICTYON AND QUININE.

When we add 1 cc. of fluidextract of eriodictyon to 0.040 Gm. of quinine hydrochloride in 1:1000 aqueous solution, the after-bitterness otherwise clinging to the palate is entirely removed and a reduction occurs in the primary bitterness, though this is not lost entirely. As a matter of fact, eriodictyon has a slightly bitter taste of its own. If the proportion of quinine is increased, the bitterness becomes quite marked and lasts for a considerable time afterward. Hence, as far as tasting experiments are concerned, 0.040 Gm. seems to be the limit of the disguising

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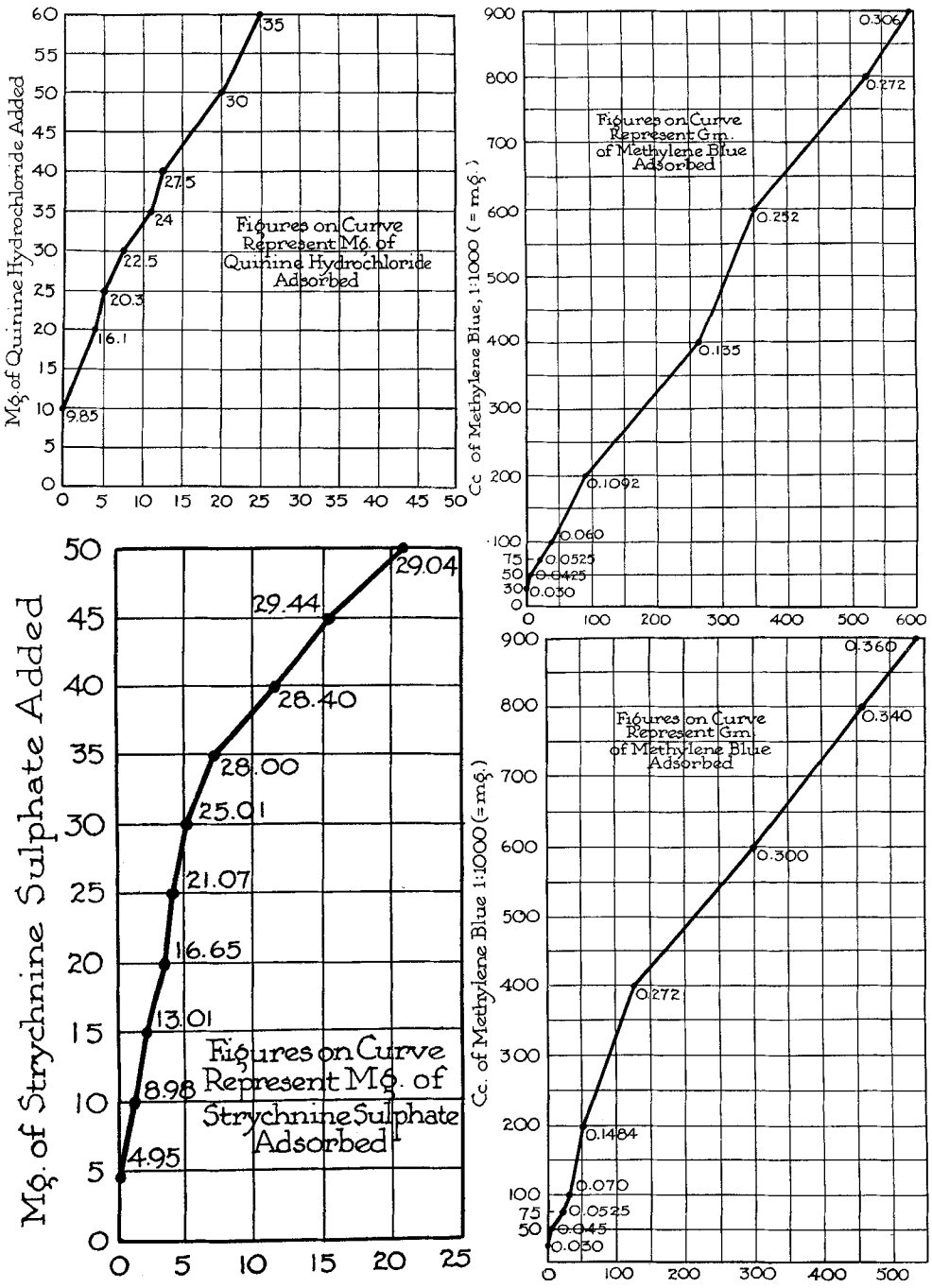

Upper, left.—Curve 1: One cc. Fldext. Eriodictyon added to varying quantities of Quinine hydrochloride in 49 cc. of water. Lower, left—Curve 2: One cc. to varying quantities of Strychnine sulphate in 49 cc. of water. Upper, right.—Curve 3: One cc. Fldext. Eriodictyon added to varying quantities Methylene Blue in 1:1000 aqueous solution. Lower, right.—Curve 4: Eriodictyon resinoid (0.33 Gm. in 5 cc. alcoholic menstruum) added to varying quantities of Methylene Blue in 1:1000 aqueous solution.

power of 1 cc. of fluidextract of eriodictyon; and this agrees with Sollman's (3) findings, and also fairly well with the following quantitative experiments.

Method of Study.—We added 1 cc. of fluidextract of eriodictyon to progressively increasing quantities of quinine hydrochloride, always made up to 50 cc. with distilled water. The mixture was well shaken and filtered. Then 25 cc. of the filtrate was tested for the amount of quinine left in solution in the following manner: it was made strongly alkaline with Ammonia T.S. and extracted with ether-chloroform (3:1) mixture, as directed in the U. S. P. Assay of Cinchona. The alkaloidal solution was evaporated to dryness and the quinine taken up in 25 cc. of acidified water. An aliquot portion of this filtrate was then diluted with water to a definite volume estimated to make it correspond in strength, as nearly as possible, with one of the following standards.

0.0010 Gm. Quinine hydrochloride in 100 cc. of water
0.0015 Gm. Quinine hydrochloride in 100 cc. of water
0.0020 Gm. Quinine hydrochloride in 100 cc. of water
0.0025 Gm. Quinine hydrochloride in 100 cc. of water
0.0030 Gm. Quinine hydrochloride in 100 cc. of water

For each 5 cc. of solution and of standard we used 1 cc. of an arseno-molybdate solution of the following composition, as recommended by E. J. Sterkin and J. I. Helfgat (4):

Equal portions of
0.12% solution of sodium arsenic acid,
2.00% ammonium molybdate solution,
2.00% hydrochloric acid.

The results obtained with the arseno-molybdate solution were checked with Mayer's Reagent from which practically the same results were obtained, excepting that the latter method is not as sensitive to small amounts of alkaloid. When using Mayer's Reagent, however, extraction with the ether-chloroform mixture was not necessary, the reagent being added directly to the filtrate in the following manner:

Exactly 3 cc. of the diluted filtrate and the same amount of comparable standard are treated alike, side by side, with 3 drops of diluted sulphuric acid and 0.5 cc. of Mayer's Reagent, and the amount of quinine present determined by comparing the density of the precipitates.

The results obtained also checked with a modified U. S. P. method, as directed for the determination of alkaloids.

When we add 1 cc. of fluidextract of eriodictyon to increasing quantities of quinine hydrochloride in 1:1000 solution, remove the precipitate by filtration, and test the filtrate as above described we obtain the following figures (Table I) which, when plotted, yield Curve 1.

TABLE I.—ONE CC. OF FLUIDEXTRACT OF ERIODICTYON ADDED TO VARYING QUANTITIES OF QUININE HYDROCHLORIDE.

Quinine Hydrochloride in Solution, Gm.	Quinine in Filtrate, Gm.	Quinine Adsorbed, Gm.
0.010	0.00015	0.00985
0.020	0.0039	0.0161
0.025	0.0047	0.0203
0.030	0.0075	0.0225
0.035	0.0110	0.0240
0.040	0.0125	0.0275
0.050	0.0200	0.0300
0.060	0.0250	0.0350

We may conclude, therefore, that quinine is not removed completely from solutions by means of eriodictyon; that, however, nearly all of it is removed, if the quantity is less than 10 mg. per 1 cc. of fluidextract; and that the quantity taken out of solution increases progressively with the increase in the quantity of quinine offered.

FLUIDEXTRACT OF ERIODICTYON AND STRYCHNINE.

When we add, to varying quantities of strychnine sulphate in 49 cc. of water, 1 cc. of fluidextract of eriodictyon, we obtain a filtrate that is practically tasteless and almost devoid of alkaloid, providing the quantity of the strychnine salt does not exceed 5 mg.: 4.95 mg. of strychnine sulphate having been removed from solution. With increasing quantities of strychnine sulphate added to the same amount of the fluidextract, we find that progressively larger quantities are removed from solution, but that larger quantities also remain as shown in Table II and Curve 2.

The strychnine determinations were made in the following manner:

We added to varying amounts of strychnine sulphate, in 49 cc. of water, 1 cc. of fluidextract of eriodictyon. We employed 25 cc. of the filtrate, made it alkaline with ammonia water and extracted with chloroform. After evaporation of the chloroform, the strychnine was taken up with a definite amount of $N/50$ sulphuric acid, and the excess of acid was titrated with $N/50$ sodium hydroxide, using methyl red as indicator; and strychnine was calculated as strychnine sulphate.

Strychnine sulphate, in quantities of 30, 40 and 50 mg., was also determined gravimetrically as a check to the above method by extracting the strychnine in the filtrate by immiscible solvents, evaporating the solvent, weighing as strychnine and calculating the sulphate.

TABLE II.—ONE CC. OF FLUIDEXTRACT OF ERIODICTYON ADDED TO VARYING QUANTITIES OF STRYCHNINE SULPHATE.

Strychnine Sulphate in Solution, Gm.	Strychnine in Filtrate, Gm.	Strychnine Adsorbed, Gm.
0.005	0.00005	0.00495
0.010	0.00102	0.00898
0.015	0.00199	0.01301
0.020	0.00335	0.01665
0.025	0.00393	0.02107
0.030	0.00490	0.02510
0.035	0.00700	0.02800
0.040	0.01168	0.02832
0.045	0.01556	0.02944
0.050	0.02100	0.02900

FLUIDEXTRACT OF ERIODICTYON AND CODEINE.

Having found that 10 mg. of quinine hydrochloride and 5 mg. of strychnine sulphate are removed from solution by 1 cc. of fluidextract of eriodictyon to a sufficient extent to make these proportions of value in disguising, codeine phosphate was experimented with as probably the third most important alkaloid; though, as far as the "extent of use investigation" is concerned, codeine actually ranks first. A few preliminary tests, which will have to suffice here, make it evident that codeine obeys the same law as the other alkaloids tested: 10 mg. of codeine phosphate being completely removed from solution, at least as far as the addition of Mayer's Reagent to the acidified filtrate would indicate. On addition of 20 mg. of codeine phosphate to 1 cc. of the fluidextract, a definite precipitate is produced in the filtrate by Mayer's Reagent.

We may conclude, therefore, that 1 cc. of fluidextract of eriodictyon is capable of disguising about

10 mg. of quinine hydrochloride
5 mg. of strychnine sulphate
10 mg. of codeine phosphate.

FLUIDEXTRACT OF ERIODICTYON AND METHYLENE BLUE.

To further acquaint ourselves with the nature of the reaction between organic bases and the fluidextract of eriodictyon, we conducted dye experiments, as the quantitative determination of alkaloids is relatively time consuming. The justification for this procedure, we believe, is furnished by the results obtained.

We added 1 cc. of fluidextract of eriodictyon to each of progressively increasing quantities of methylene blue in 1:1000 solution, and estimated colorimetrically the amount of methylene blue that passed through in the filtrate. Up to 0.030 Gm. per 1 cc. of fluidextract of eriodictyon, the methylene blue is almost completely removed from solution. Above this point, progressively larger quantities appear in the filtrate, although the power of holding the dye increases with increase in the quantity of dye offered, as shown in Table III and plotted in Curve 3.

TABLE III.—ONE CC. OF FLUIDEXTRACT OF ERIODICTYON ADDED TO VARYING QUANTITIES OF METHYLENE BLUE IN 1:1000 AQUEOUS SOLUTION.

Methylene Blue in Solution, Gm.	Methylene Blue in Filtrate, Gm.	Methylene Blue Adsorbed, Gm.
0.030	Too light to read	0.0300 (almost)
0.050	0.0075	0.0425
0.075	0.0225	0.0525
0.100	0.0400	0.0600
0.200	0.0908	0.1092
0.400	0.2650	0.1350
0.600	0.3480	0.2520
0.800	0.5280	0.2720
0.900	0.5400	0.3060

That we have to deal here with a case of adsorption rather than of chemical union, may be concluded from the fact that the removal of the base from the solution is not complete in any proportion and that, within limits, the quantity removed from solution increases with increasing quantity of dye. We also found that slight modifications in technic produce unproportionately great changes in the results. That we have to deal here with a very loose combination of base and eriodictyon principles, is shown by the fact that the dye or the alkaloid, as the case may be, is readily dissolved out by $N/20$ hydrochloric acid, leaving a resinous material behind. The precipitate is also easily dissolved by alcohol, as well as by very dilute alkali ($N/100$, even $N/1000$). This makes it very evident that the alkaloidal compound will be broken up by the digestive juices, liberating the alkaloid for absorption into the blood.

THE "ACTIVE PRINCIPLE" OF ERIODICTYON.

That the "resinoid" is the active agent is shown by the fact that practically the same degree of activity resides in the resinoid, which may be obtained by adding

the fluidextract of eriodictyon to an excess of water, collecting the precipitate on filter paper, washing and drying. The yield is 0.33 Gm. per 1 cc. of the fluidextract. This resinoid redissolved in the menstruum (alcohol, 4 volumes, and water, 1 volume) is as efficient in removing methylene blue from solution as the equivalent amount of fluidextract, as shown by Table IV and Curve 4. To obtain such results, however, we must use a more dilute solution of the resinoid in order to secure as efficient, evidently as colloidal, a precipitate as is yielded by the undiluted fluidextract. Presumably some of the other ingredients in the fluidextract favor colloidal dispersion of the resinoid from the more concentrated solution. It is only when there is a great excess of resinoid, about ten times the weight, that it removes the dye almost completely from solution. It adsorbs more dye with the increase in the amount of dye; leaving, however, a larger quantity of unadsorbed dye in solution.

TABLE IV.—ONE CC. OF A SOLUTION OF 0.330 GM. OF RESINOID IN 5 CC. OF ALCOHOLIC MENSTRUUM IS ADDED TO VARYING QUANTITIES OF METHYLENE BLUE IN 1:1000 AQUEOUS SOLUTION.

Methylene Blue in Solution, Gm.	Methylene Blue in Filtrate, Gm.	Methylene Blue Adsorbed, Gm.
0.030	Too light to read	0.0300 (almost)
0.050	0.005	0.045
0.075	0.0225	0.0525
0.100	0.030	0.070
0.200	0.0516	0.1484
0.400	0.128	0.272
0.600	0.300	0.300
0.800	0.380	0.320
0.900	0.540	0.360

That this adsorption is based on electric charges—the resinoid being electronegative and attracting the electro-positive base—is shown by the fact that an acidic dye like eosin is not removed in any appreciable amount from solution by the fluidextract of eriodictyon; nor does eriodictyon seem to lessen the taste of such acidic body as phenobarbital. This specific adsorption relation also explains why the other taste sensations, that of sour, salty or sweet are not diminished by eriodictyon; and it is evident that *only the bitter taste of bases is disguised by it.*

That the resinoid is *the* active principle in the disguising of quinine is also shown by the negativeness in this respect of the other two proximate principles of eriodictyon studied, as reported above.

THE AROMATIC SYRUP OF ERIODICTYON.

The aromatic syrup of eriodictyon is a relatively popular preparation, as is shown by its scoring a usage of 11 per 10,000 prescriptions in the "U. S. P.-N. F. Prescription Ingredient Survey" completed by Professor E. N. Gathercoal. This is equivalent to an annual usage in prescriptions in the United States of 275,000 to 300,000 times.

Our study of the syrup indicates that it richly deserves this popularity: That, indeed, it is probably not as popular as it ought to be. It is interesting to note that the percentage of alkali (0.125%) contained in it is barely sufficient to maintain the resin in solution; and that it is quite fortunate the amount is not larger for we have found that a doubling of the percentage of alkali would be sufficient to dissociate the quinine adsorption product, thereby destroying the utility of the syrup for the disguising of the alkaloid.

In view of the fact that the syrup contains a relatively small amount of eriodictyon, 10 cc. of syrup being equivalent to 0.32 cc. of the fluidextract, one might anticipate a relatively restricted disguising power for quinine. If 1 cc. of the fluidextract disguises 0.040 Gm. of quinine hydrochloride, then 10 cc. or about two teaspoonfuls of the syrup might be expected to disguise only 0.013 Gm. of quinine hydrochloride, which is indeed the case. This, however, is so very minute a dose, as to be of no practical importance.

When we increase the amount of quinine in the form of hydrochloride, an offensive bitterness appears; and the precipitate, being very light, separates and rises to the top. It is possible to disguise a much larger amount of quinine in form of the alkaloid. In this case, too, the precipitate is light and rises to the top. It is a curious fact that the precipitate formed by the addition of quinine sulphate is, in contradistinction to the others, heavier; and has but a slight tendency to separate. It is also possible to introduce considerably more—as much as 0.050 Gm. of quinine sulphate per 5 cc. of the syrup—without the development of more than a moderate degree of bitterness. In other words, quinine sulphate gives the best mixture with syrup of eriodictyon: a mixture that stands up better than either of the two other forms of quinine experimented with; and the bitterness of the preparation is not any greater than that resulting from the use of quinine alkaloid. However, with a 1% suspension of quinine sulphate the practical limit of the disguising power of this syrup is reached.

As this is still rather too small a dose of quinine for the treatment of malaria, we experimented with quinine ethyl carbonate (euquinine) and diquinine carbonate (aristochin); and find that it is possible to suspend as much as 0.30 Gm. of either of these per teaspoonful of the syrup with the production of an actually delicious dose, with but a slight tinge of immediate bitterness and no after-bitterness whatever. We, therefore, recommend the following prescription as the best disguised liquid administration form of quinine known to us.

℞	Quinine ethyl carbonate	5.00 Gm.
	Aromatic syrup of eriodictyon, to make	60.00 cc.
	M. Label: Teaspoonful every four hours.	

This preparation is much more palatable than cacao syrup-quinine preparation, which, though quite free from immediate bitterness, leaves a long lingering bitter taste behind.

In attempts at improving or simplifying the manufacture of the syrup, we have prepared it with various modifications: using various proportions of alkali, compound spirit of cardamom, as well as compound spirit of orange; but have failed to secure any improvement by these means upon the official formula.

In the disguising of codeine, the syrup is also of practical value, at least for children's dosage. Thus, the following prescription is deliciously sweet, with but a slight tang of initial bitterness, and no after-bitterness whatever.

℞	Codeine phosphate	0.10 Gm.
	Aromatic syrup of eriodictyon, to make	60.00 cc.
	M. Label: Teaspoonful with water every two to four hours as required.	

In the disguising of strychnine, the aromatic syrup of eriodictyon is still more

efficient, because the therapeutic dose of strychnine is so much smaller. While an adult dose of 1 to 2 mg. overtaxes its disguising power, a dose of $^1/_4$ to $^1/_2$ mg. is well covered.

℞	Strychnine sulphate	0.015 Gm.
	Aromatic syrup of eriodictyon, to make	120.00 cc.

M. Label: Teaspoonful in water three times a day after meals.

It will be found that the dose of strychnine as well as of quinine that is present in the Elixir Iron, Quinine and Strychnine could be much more pleasantly administered with the Aromatic Syrup of Eriodictyon, instead of Aromatic Elixir as the vehicle. Unfortunately, iron cannot be added to this mixture, owing to "ink" formation, due to combination obviously with the tannic acid present. Attempts at detannating the eriodictyon have thus far not been successful.

There is no doubt that other alkaloids can be disguised in a similar manner; and we hope to pursue this question at a future time.

INCOMPATIBILITIES.

It must be realized that the syrup of eriodictyon is a very delicately adjusted preparation, and that it is—and must be—slightly alkaline in reaction. It is, therefore, incompatible with acids and acid salts. It is also incompatible with alkalies, as an excess of alkali dissociates the alkaloid-resin compound. Iron salts constitute another important incompatibility. Oxidizing and reducing agents are, of course, also taboo.

AROMATIC ELIXIR OF ERIODICTYON.

The aromatic elixir of eriodictyon is hardly prescribed at all. This is not to be wondered at when we contemplate the fact that the elixir, as at present constituted, is a very unstable preparation: becoming cloudy soon after its preparation and having a tendency to progressive precipitation upon standing. It also offers a curious example of pharmaceutic redundancy, containing no less than fifteen ingredients. As it should be a fundamental principle of medicinal combination that each ingredient must have a reason for its presence in the formula, we may cogently ask, why the fluidextract of taraxacum, admittedly a bitter drug, is contained in a preparation, the accepted purpose of which it is to serve for the disguising of the bitter taste? Also, why should glycyrrhiza be used in its preparation, when this is largely precipitated out by the alcoholic menstruum. And yet the menstruum is not sufficiently alcoholic to keep the resinoid, the active principle of eriodictyon, in solution: so that an undetermined quantity is unceremoniously filtered out and some of it continually separates on standing, as previously noted. For all these reasons we believe that the aromatic elixir of eriodictyon should be deleted from the National Formulary.

CONCLUSIONS.

1. The "active principle" of eriodictyon, as far as the disguising of quinine, codeine or strychnine is concerned, is the resin.

2. The resin acts by a process of adsorption, which is specific for bases only, as is evidenced by positive results with alkaloids and basic dyes and negative results with acids and with an acidic bitter substance, such as phenobarbital.

3. Only the bitter taste of basic bodies, given in very small doses (*e. g.*, strychnine) or of slight bitterness (*e. g.*, quinine ethyl carbonate) can be satisfactorily disguised by eriodictyon.

4. The aromatic syrup of eriodictyon is an elegant preparation, for which we cannot suggest any improvement.

5. The aromatic elixir of eriodictyon, on the other hand, is a very unstable and unsatisfactory preparation; and, as it is hardly prescribed at all, we recommend its deletion from the National Formulary.

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PEYOTE—THE DIVINE PLANT OF CERTAIN INDIAN TRIBES.*

BY JOHN THOMAS LLOYD.

Peyote or Mescal Buttons, known also by a number of other names, in the words of Louis Lewin—"towers above the rest of known plants on account of its special effects on man. No other plant brings about such marvelous functional modifications of the brain."

Peyote is a species of cactus (Anhalonium lewinii). When fresh the top is fleshy, gray-green in color, and dome-shaped, usually about an inch and a half in diameter. The root is long and tapered, resembling the root of a parsnip. For use, the tops are removed and dried. In this condition they are brown and greatly shrunken.

The plant occurs locally over a considerable part of the Mexican Plateau, and extends north of the Rio Grande, into Texas.

Accounts of the influence of Peyote on the human mind have appeared in a few publications. These agree in their descriptions of the pleasing brilliancy of color and the fantastic forms of objects seen under the effect of the drug.

By the Indians, the plant has been known for untold generations, and worshipped as the "vegetable incarnation of the Divinity." It is known not alone to the Indians of the regions it inhabits, but also to tribes as far West as the Pacific, and northward to Wyoming and Nebraska, while Indians from Oklahoma make annual pilgrimages to Texas to gather their supply for worship. Naturally, the use of Peyote was condemned and forbidden by the early missionaries, while later it attracted the attention of officials concerned with Indian affairs, under whose influence a prohibitory law was enacted against the use of the drug. This law is apparently as effective as other laws designed to change religion, or modify established customs.

The present article is written to record visions and hallucinations experienced by the writer while in the region of Mexico in which Peyote grows, and among the Indians who use it. These hallucinations, following an Indian dance around a fire, as is customary in the Peyote ceremony, were so fantastic and vivid that he

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