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NOTES UPON INDIAN EPHEDRAS.

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With the occurrence of several species of Ephedra in Western Tibet and Northern India it was thought that here lay a further possible supply of crude material for the production of ephedrine. However, seeing that not all species of ephedra contain ephedrine, and that in others the chief alkaloid present is the isomer pseudoephedrine it was thought to be of importance to make a chemical analysis of the Indian Ephedras. Books (1), (2) upon Indian materia medica list two ephedras, *E. vulgaris* and *E. pachyclada*, under the Persian name "Huma," and other names which are not familiar. It is considered to be the Soma of the Vedas. A personal visit to the Forestry Department at Dehra Dun revealed the fact that in Northern India there are three common species of ephedra and several varieties of the same. *Ephedra intermedia*, *E. Gerardiana*, and *E. foliata*, the last mentioned growing on the plains.

ANALYSES.

With the samples kindly supplied we have undertaken in our Peking laboratories identical examinations for the alkaloids to those done upon Chinese Ephredas and published from time to time. The sample of *Ephedra intermedia* was sufficiently large to allow of our doing numerous analyses upon the various parts of the stem, the dry brittle stems loose in the package giving slightly higher values. The methods used were as recently published (3), number 3 by direct alkalinization being found most suitable for regular assay work. This was checked with further analyses by modified methods. The percentage of alkaloid present was calculated from the acid titration values, the titrated solutions being subsequently tested by the "Biuret Test" (4) for the relative percentages of ephedrine and pseudoephedrine. The identity of these two isomers in the case of *Ephedra intermedia* was conclusively confirmed by the preparing of their hydrochloride salts with their characteristic melting points and optical rotation. Having but small samples of *Ephedra Gerardiana* the identity of the alkaloids depended on the Biuret reaction, which is quite reliable and final for practical purposes. The results are shown in Table I.

TABLE I. ASSAY OF INDIAN EPHEDRAS.

Species of Ephedra.	Total alkaloid $C_{10}H_{15}ON$.	Biuret test. Ephedrine.	Pseudo-ephedrine.	Percentage in plant. Ephedrine.	Pseudoephedrine.
1. *Ephedra Intermedia*					
(*a*) Dry broken stems	1.17%	30 to 40%	60 to 70%	0.351 to 0.468	0.702 to 0.819%
(*b*) Unbroken stems	1.14%	30 to 40%	60 to 70%	0.342 to 0.456	0.684 to 0.798%
Average	1.155%	30 to 40%	60 to 70%	0.347 to 0.462	0.693 to 0.809%
2. *Ephedra Gerardiana*	1.65 to 1.70%	70 to 80%	20 to 30%	1.17 to 1.34	0.335 to 0.505%
Ephedra sinica	1.315%	80 to 85%	15 to 20%	1.052 to 1.118	0.197 to 0.263%
Ephedra equisetina	1.754%	85 to 90%	10 to 15%	1.49 to 1.579	0.175 to 0.264%

Isomers and Other Assays.—The results of these assays for *Ephedra Gerardiana* are about as high as the best figures obtained from *Ephedra equisetina* (5), but the relative amount of ephedrine is not quite as good. The latter yielded 85 to 90% of the total alkaloid as ephedrine, making the ephedrine content of mature *E. equisetina* 1.49 to 1.58% as compared with 1.17 to 1.34% for *E. Gerardiana*. The very large amount of pseudoephedrine in *E. intermedia* does not disqualify it as a possible source of ephedrine, because the conversion of the one isomer to the other is, up to 50%, quite a simple operation. In spite of the reported discovery of other isomers in Chinese Ephedras the amounts present are so small as to be insignificant, such might be obtainable from the mother liquors of Indian ephedras extracted in large bulk, but it is not to be expected that they are present in any large amounts.

Differences in Species.—The various species of Ephedra show gross morphological differences chiefly concerning the woody or herbaceous character of the stems (5), the length and weight of the nodes, the number of nodes or joints, etc. The sample of *Ephedra intermedia* was critically examined upon these points. Table II shows the average length, weight and number of internodes in this species. The longest stem measured 26 cm., the average length was 7.74 cm. This does not refer to the main stems which were woody and known to contain practically no alkaloid. In *Ephedra sinica* it has been shown that the nodes or joints of the stems contain a greater amount of pseudoephedrine than the internodes (6), hence the number of joints or in other words the length of the internodes in each species may have a bearing on the proportions of the isomers present.

The sample of *E. intermedia* contained many broken dry pieces which averaged only 25 mg. for the weight of each internode, and 24 mm. in length, this would be due to dryness, also to the fact that these pieces were terminal parts of growing stems. Nearly two thousand short pieces of about one nodal length were examined, and none showed the weight or length of the more complete samples.

Seasonal Variation.—These analyses need a further note with regard to seasonal variation. Chinese ephedras, in autumn contain three times as much ephedrine as in spring (7). It is not impossible that there are to be obtained more favorable samples than those examined. Indian artemesias show greater seasonal variation in santonin content, and ephedra may also show big differences.

Therapeutic Significance.—The very great difference in the alkaloids occurring in *E. intermedia and E. Gerardiana* show plainly that they are not likely to yield identical physiological effects. The former containing so much pseudoephedrine is not likely to produce such favorable results on the respiratory passages, or tissue shrinkage. It seems quite incorrect to classify several species together as one drug, as has been done by Nadkarni. Pseudoephedrine has been shown to

TABLE 2. ASSAY OF A SAMPLE OF MAHUANG FROM DEHRA DUN, EPHEDRA INTERMEDIA

Length of stems. Cm.	No. of stems.	Total length. Cm.	No. of internodes.	Average length of internodes. Mm.	Total weight. Gm.	Average weight of internodes. Mg.
2	21	42	24	18	0.59	24.6
3	43	129	60	22	1.49	24.8
4	40	160	70	23	1.88	26.9
5	50	250	93	27	3.25	35.0
6	72	432	160	27	5.59	35.0
7	48	336	120	28	4.52	37.7
8	24	192	64	30	2.72	42.5
9	23	207	69	30	3.04	44.0
10	22	220	71	31	3.21	45.2
11	15	165	54	31	2.52	46.7
12	17	204	63	32	3.04	48.2
13	13	169	53	32	2.59	48.9
14	13	182	56	33	2.74	48.9
15	5	75	23	33	1.20	52.2
16	9	144	43	33	2.30	53.5
17	6	102	27	38	1.51	55.9
18	5	90	24	38	1.39	57.0
19	3	57	15	38	0.91	60.6
20	5	100	28	36	1.83	65.4
21	3	63	18	35	1.21	67.2
22	1	22	6	37	0.42	70.0
23	1	23	7	33	0.60	85.7
24	1	24	7	34	0.65	92.9
25	0	0	0			
26	1	26	8	32	0.80	100.0
	441	3414	1163	30	50.00	43.0
Ephedra sinica				35.4	..	21.3
Ephedra equisetina				19.2	..	13.1

have under certain circumstances an opposite effect to ephedrine upon vasoconstriction, and its blood pressor action is more musculotropic than neurotropic and the reverse is true for ephedrine.

Comparison with Other Assays.—Chopra (8) and his co-workers in Calcutta have recently reported upon these Indian Ephedras and state that *Ephedra Gerardiana* Wall (syn. *E. vulgaris*, Rich. and *E. distachya*, linn.) contains in the green twigs 1.49% total alkaloids in which they reckon 1.06% is pure ephedrine. This result is similar to our own obtained from a slightly better sample.

Further they analyzed *Ephedra intermedia*, Schrenk and Mey (synonym *E. pachyclada*, Boiss.), and found 1.8% total alkaloids in the green twigs and 1.16% in the mixed stems and twigs, in which they report 1.058% and 0.682%, respectively, of ephedrine. This is greatly divergent from our most favorable result which gave 0.351% of ephedrine in a total alkaloidal content of 1.17%. After assaying our material we purified and recrystallized our alkaloids obtaining from each hundred grams of crude drug 0.18 Gm. of pure ephedrine hydrochloride melting at 215–216° C. and 0.39 Gm. of pure pseudoephedrine alkaloid melting at 118° C., which closely approximate the ratio of these two alkaloids 30% to 70% as observed by our Biuret assay method. Examination of our mother liquors from the various crystallizations showed the presence of the residual amounts of alkaloids.

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AN UNUSUAL FACTOR INFLUENCING ACTION OF SOME DRUGS ON SMOOTH MUSCLE.

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INTRODUCTORY.

The study of the action of a drug from a broad pharmacological point of view is vastly more complicated than is generally appreciated by the clinical practitioner and even by specialists in other fundamental medical sciences. One of the most important phases connected with a complete pharmacological study of the drug is the necessity for the investigation of various *conditions* affecting the action of such a compound. The conditions influencing the action of drugs are of a three-fold nature. They may depend upon the drug itself, as for instance the dose of the reagent administered, its concentration, its method of administration, etc. Again they may depend upon the patient or animal to which the drug is administered. Thus for instance, the age of the animal may play an important rôle apart from the dosage; the condition of the subject whether normal or pathological may make a great difference in its reaction to the drug, etc. Not only may the action of a drug vary with individual subjects but even various organs and indeed parts of the same organ may respond differently to one and the same pharmacological agent. Thus Young and Macht have shown that the smooth muscle tissue of the *trigonum vesicae* responds very differently to certain sympathetic and para-sympathetic drugs from the smooth muscle of the fundus of the same bladder (1). Again the difference in response between pathologic and normal tissues has been well illustrated by the researches of Macht and Ting who found that the bronchi of pigs respond differently to Epinephrine, Pilocarpine, Atropine and the other pharmacological reagents when the animals suffer from bronchial pneumonia as compared with the response of the bronchial muscle from normal pigs' lungs (2). Finally, in the third place, the action of drugs may be profoundly influenced by certain external conditions. For instance, the room temperature may markedly affect the action of a drug as is the case with injections of Colchicine in frogs; ultraviolet rays increase the potency of Quinin and Quinidin Sulphate injections in rats as shown by Macht and Teagarden (3), and polarized light was found by the present author to affect the convulsions produced by camphor to a greater degree than non-polarized light of the visible spectrum of exactly the same intensity (4). All these various factors concerned in drug action have been discussed by the author elsewhere (5). The present note is intended