ion concentration increases just the same as the concentration of the salt itself increases. Whereas, when you have the silver proteid the largest part of the silver ions are forming some chemical complex or colloidal complex with the proteids present, and so they don't irritate the tissues in the body.

H. B. Corbitt: You state that there is silver colloid there in the colloidal dispersion. In such a state I believe it could be carried to any part of the body, say, to the face, and might be deposited under the skin. Does the sunlight affect it? Do you know of any cases of argyria?

Dr. Kolthoff: When you take silver nitrate it is reduced in the body to metallic silver, and the metallic silver deposits in the cells just under the skin, but it is not sunlight which plays the rôle but only special characteristics of the cells of the skin that are doing that, because it is not only in the skin that you have metallic silver but also in other cells of the body. I am not quite sure where all these cells are because I am not a pharmacologist, only a chemist and pharmacist. The main part is deposited in the cells just under the skin.

A PHARMACOGNOSTIC AND CHEMICAL STUDY OF MA HUANG (EPHEDRA VULGARIS VAR. HELVETICA).

BY K. K. CHEN.*

I. INTRODUCTION.

In a preliminary report of experiments with Ma Huang (1) it was noted that the drug possessed actions very similar to those of adrenaline, and that these were due to an alkaloid which had been identified as Ephedrine. A more complete report of these experiments and of the results of administration of ephedrine to normal and diseased men has been published (2). It appears from the pharmacodynamic studies that ephedrine is of considerable value as a circulatory stimulant in surgical shock, as a bronchodilator in asthma, as a mydriatic, and as an apparently specific remedy in Addison's disease. Since ephedrine is effectively absorbed from the gastrointestinal tract, and since solutions of the alkaloid are very stable, it appears to be a drug of definite clinical value. Naturally the identification of the plant and alkaloid is of some importance.

II. HISTORY.

Ma Huang has been identified as *Ephedra vulgaris* var. *helvetica*, family *Gnetaceae* (3). In Chinese characters, *Ma* means "astringent" and *Huang* "yellow;" the former probably refers to taste and the latter to color after storage. It was tasted and placed by Emperor Shen Nung some 5100 years ago in the "medium class" (4). It entered many famous prescriptions, and appeared in "Pentsao Kang Mu," the Chinese Dispensatory written in 1596 A.D. (5). No scientific investigation was made until Nagai (6) isolated an alkaloid from it which he named ephedrine. Its empirical formula is $C_{10}H_{15}ON$; its chemical structure has been repeatedly studied (7) (8) (9) and is most probably phenyl-ol *1*-methyl *2*-methyl-amino *2*-ethane, $C_6H_5OH.CH.CH.CH_3.NHCH_3$.

III. GEOGRAPHICAL DISTRIBUTION.

The exact distribution of the plant requires an accurate survey. It has been reported that in China it is indigenous to the sea coast (3), to west Szechuan near

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Tachienlu (10), and to several districts of Kansu, Shensi, Honan, Shangtung and Kiangsu Provinces (5). In central Europe, the plant was known to have originated from the Orient, and the Mediterranean basin (11). The European variety is, however, not the same as the Asiatic for the alkaloid isolated and named pseudoephedrine by Merck (12) is isomeric but not identical with Ephedrine.

Fig. 1.—Ma Huang, Ephedra vulgaris, var. helvetica.

IV. DESCRIPTION OF THE PLANT.

Ephedra vulgaris var. helvetica is a low, dioecious, practically leafless shrub, 60–90 centimeters high (Fig. 1). The stem, green in color, is slender, erect, somewhat ribbed and channelled, 1.5 millimeters in diameter, and usually terminating in a sharp point. On the stem there are nodes, 4–6 centimeters apart, at which the leaves appear as whitish, triangular, scarious sheaths. Branching occasionally takes place at the nodes. The plant blossoms in the summer. It is sold by the native drug stores in the form of dried brownish green sticks, 1–1.5 centimeters long, known as Ma Huang.

V. HISTOLOGY OF THE STEM.

A transverse section (Fig. 2) made from the dried specimen shows that it is somewhat circular or elliptical in shape with ribbed edges. The epidermis (Ep.) consists of a single layer of cells, the radial diameter of each cell measuring 22–24μ and the tangential one 20–24μ. The outer wall is much thicker than the others, its cellulose layer being 4μ, while the cutinized layer is 6μ, in thickness. A cuticle covers the surface. At the apex of the ribs certain cells have their cutinized walls swollen including some cellulose forming trichone-like projections. The cytoplasm of all the epidermal cells appears to occupy a rectangular space. A number of stomata are found between these cells. The remaining cortical region is made of several layers of thin-walled parenchymatous cells (Par), polygonal in shape, varying from 14–36μ in diameter and containing chloroplasts and simple sugars which can be demonstrated microchemically. Their nuclei can be stained by safran and measure about 7μ in diameter. Here and there they are intermingled with air spaces (A) and islands of bast fibers (B). The latter are angular and thick-walled, and measure 14–20μ in diameter. The vascular bundles, ten in number, wedge-shaped with apex pointing to the center, belonging to the open, collateral type, are just next to these parenchyma cells. The phlœm consists of bast fibres, not much different from those in the outer region, phlœm parenchyma and cambium cells

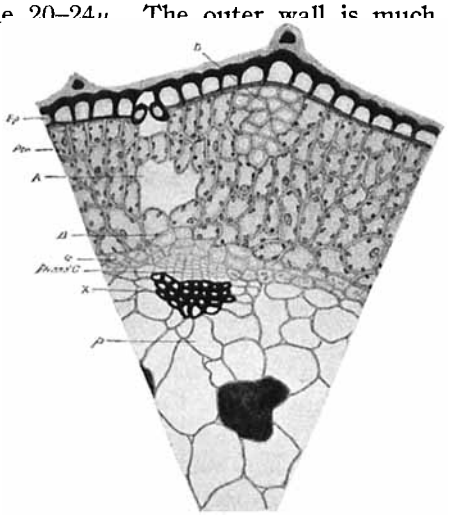

Fig. 2.—Transverse Section of the Stem of Ma Huang. Ep, Epidermis with a stoma. B, bast fibres. Par, parenchyma with chloroplasts. A, air space. Ph and C, phlœm parenchyma and fascicular cambium. Ic, interfascicular cambium with starch granules. X, xylem. P. pith.

(Ph and C) which are thin-walled and measure only about 6–8μ in diameter. The xylem (X) consists of thick-walled cells. Their radial diameter, 10–12μ, is greater than their tangential diameter, 7μ. The interfascicular cambium (Ic) joins the fascicular cambium to form a continuous ring. These cells as well as the neighboring parenchyma cells contain starch granules which can be stained blue with iodine solution. The cells of this portion of the cambium are larger than those in the fascicular cambium, being 12–16μ thick, 32μ wide. The center of the stem constitutes the pith (P), consisting of rather round, large, dead cells, measuring 70μ or more in diameter, and sometimes containing a homogeneous brown substance of unknown nature. Intercellular spaces are of frequent occurrence.

A longitudinal section of the stem (Fig. 3) shows the epidermis (Ep) as a layer of elongated cells, varying from 72 to 94μ in length. The bast fibres (B) are too long for microscopic measurement. Their ends are rather blunt. The chlorophyll-bearing parenchyma (Par.) looks very much like the spongy layer of a leaf. The cells in the phlœm parenchyma are longer than those in the cambium, being 100μ instead of 56μ. The xylem portion (X) consists of spiral (Sp.) and pitted (not shown) vessels, and tracheides (Tr) with bordered pits. Some of the tracheides are 286–300μ long. The shortest pith cells (P) measure 280μ in their longitudinal diameter.

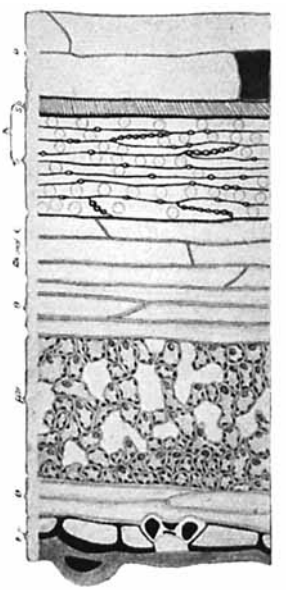

Fig. 3.—Longitudinal section of the stem of Ma Huang. Ep, Epidermis with a stoma. B, bast fibres. Par, parenchyma resembling spongy layer of a leaf. Ph and C, phloem parenchyma and fascicular cambium. Sp. spiral vessel. Tr, tracheides with bordered pits. X, xylem. P, pith.

VI. EPHEDRINE, THE ALKALOID OF MA HUANG.

(a) *Isolation*.—This active principle can easily be isolated by means of immiscible solvents. The most satisfactory procedure was as follows: The drug was ground to No. 40 powder and percolated with 80% alcohol until the percolate was colorless. The percolate was distilled on a water-bath under diminished pressure at about 52° C. until a syrupy fluid was obtained. The latter was diluted with water, rendered alkaline with ammonium hydroxide, and filtered. As it was found that the alkaloid is soluble in water, the filtrate was shaken with chloroform twice, while the residue on the filter was extracted twice with the same solvent on a water-bath connected to a reflux condenser for an hour or more. The combined chloroform extract was subjected to distillation until a small volume was obtained, and then left to spontaneous evaporation. The greenish, fragrant gelatinous residue was dissolved in a small volume of hot water and treated with dilute hydrochloric or sulphuric acid until exactly neutral to litmus paper. After evaporation on the water-bath, the residual alkaloidal salt was dissolved in a minimum volume of absolute alcohol and crystallized out by chilling in a mixture of salt and ice, ether being added to hasten and complete the crystallization. It was purified by recrystallization from alcohol three times. The alkaloid itself can be regenerated by making the salt solution definitely alkaline with ammonium hydroxide and shaking and

crystallizing out from chloroform. It appears as white rosette crystals easily broken up into coarse needles, its hydrochloride as fine white needles, and its sulphate as white, plate-like, rhombic crystals. We tried to shorten the process of preparation by mixing the sticks sold on the market with slaked lime and extracting with alcohol on the water-bath connected to a reflux condenser to save the trouble of powdering and percolation, but we found that the yield of alkaloid was less satisfactory.

(b) *Identification.*—The physical constants of the base and its salts we have found to be as follows:

	Melting point.	Specific rotation.
Ephedrine	210° C.	—
Ephedrine HCl	214° C.	$[\alpha]_D^{25} - 35°$ (in water).
Ephedrine H_2SO_4	242° C.	

The melting points of the base and its hydrochloride are in perfect agreement with the figures obtained by Nagai (13).

(c) *Reactions towards alkaloidal Reagents.*—The results are shown below and need no explanation:

Reagent.	*Result.*
Mayer's	Cloudy on standing
Wagner's	Orange precipitate
Phosphomolybdic acid	Greenish yellow heavy precipitate, blue on standing
Phosphotungstic acid	Heavy white precipitate
Erdmann's	Yellow ring below, pink ring above and smoky pink layer on top
Concentrated H_2SO_4	Same as Erdmann's
Concentrated H_2SO_4 + $K_2Cr_2O_7$	Bluish green, turning brown
Tannic acid	No color change or precipitate
Picric acid	No color change or precipitate
Concentrated HNO_3	No color change or precipitate
$FeCl_3$	No color change or precipitate.

(d) *Assay.*—This was performed volumetrically by following the method of Assay of Belladonna Root given in U. S. P. IX (14). In the first step we used a mixture of chloroform, 1 volume, and ether, 3 volumes, and finally employed methyl red as the indicator instead of cochineal. Each cubic centimeter of $N/10$ H_2SO_4 used corresponds to 16.513 milligrams of ephedrine. From three different samples of crude drug, we obtained the following figures:

Sample 1	Ephedrine 0.01858% average of 3 determinations
Sample 2	Ephedrine 0.07214% average of 3 determinations
Sample 3	Ephedrine 0.09082% average of 3 determinations

The duplicate determinations checked very well. It appears that the content of the alkaloid is small and varies considerably.

VII. DETERMINATION OF MOISTURE, VOLATILE SUBSTANCE AND ASH CONTENTS.

Four grams of No. 60 powder were weighed in a tared crucible, previously heated to constant weight, and placed in a desiccator until there was no more loss

of weight. The difference is the amount of moisture in the powder. The contents were then put on a water-bath until constant weight was reached. This second difference represents the amount of volatile substances. The powder was then incinerated in an electric muffle furnace and the weight of ash determined. The following data were obtained from different samples of the crude drug:

Sample no.	Determination no.	Moisture in %. Individual.	Moisture in %. Average.	Volatile substances in %. Individual.	Volatile substances in %. Average.	Ash in %. Individual.	Ash in %. Average.
	1	4.607	.....	1.750	.....	7.350	.....
I	2	4.570	4.569	1.815	1.796	7.295	8.315
	3	4.530	.....	1.825	.....	7.300	.....
	1	.....	.....	.....	.....	8.397	.....
II	2	.....	.....	.....	.....	8.374	8.399
	3	.....	.....	.....	.....	8.427	.....
	1	.....	.....	.....	.....	8.280	.....
III	2	.....	.....	.....	.....	8.378	8.352
	3	.....	.....	.....	.....	8.399	.....
IV	1	.....	.....	.....	.....	8.350	8.350

The moisture and volatile substances vary with climate. In Peking where the weather is dry, especially in winter, one would look for a low percentage, while in Shanghai where the weather is damp one would expect it to be higher. The percentage of ash seems to be more constant, about 8.5%.

VIII. ANALYSIS OF ASH.

Besides the water soluble, acid soluble (in 10% hydrochloric acid) and insoluble portions, we have analyzed the individual common elements of the ash. For sampling, 10 grams of the powdered drug were ignited, and the ash was treated with concentrated nitric acid to precipitate silicates. After evaporation to dryness the residue was dissolved in dilute nitric acid and made up to 250 cc. Aliquot portions were taken for investigation of these elements. Chlorine was determined by Volhard's method, sulphur by precipitation as barium sulphate, phosphorus colorimetrically by Briggs' modification of Bell-Doisy's method (15), calcium by precipitation with ammonium oxalate ignited and weighed as calcium oxide, potassium by precipitation with platinic chloride, weighed as potassium chloroplatinate, and sodium by the difference calculated from the total weight of potassium and sodium chloride previously determined. Duplicates were made from separate ash samples. The results are shown in the following table:

Analysis for	Determination no.	Individual % of ash.	Average % of ash.
	1	21.600	.....
H_2O soluble ash	2	18.610	20.260
	3	20.580	.....
	1	60.310	.....
HCl soluble ash	2	63.090	60.960
	3	59.470	.....
	1	18.100	.....
Insoluble ash	2	18.290	18.780
	3	19.950	.....
	1	0.257	.....
Chlorine	2	0.254	0.271
	3	0.302	.....
	1	1.643	.....

Analysis for	Determination no.	Individual % of ash.	Average % of ash.
Sulphur	2	1.602	1.608
	3	1.578	.....
	1	2.047	.....
Phosphorus	2	2.023	2.022
	3	1.995	.....
	1	30.180	.....
Calcium	2	31.190	30.500
	3	30.120	.....
	1	3.129	.....
Potassium	2	3.399	3.456
	3	3.840	.....
	1	9.055	.....
Sodium	2	8.725	8.886
	3	8.877	.....

Iron and manganese were also present in small amount, but were not determined quantitatively.

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JOHN SIMON GUGGENHEIM MEMORIAL FOUNDATION.

Former U. S. Senator Simon Guggenheim, of Colorado, has made a preliminary gift of $3,000,000 for establishing a fund which will support fellowships for research. The provisions are somewhat along the lines of the Rhodes scholarships, however, intended for men and women who have demonstrated creative power in science and the arts. The stipend will be approximately $2500 a year, and it is expected that after the first year between 40 and 50 scholarships will be maintained. The appointees must have shown marked ability in their special fields. Professors on sabbatical leave, or individuals holding other fellowships, will be eligible, as well as other candidates. The Secretary of the Foundation is Henry Allen Moe, and may be addressed at 120 Broadway, New York.