Rauvolfia serpentina—*Its History, Botany and Medical Use*

This small shrub, native to the Orient from India to Sumatra, has for centuries been used in Indian medicine. In 1952 reserpine, one of several alkaloids in the plant, was isolated from its root and has since been evaluated in western medicine as one of the most valuable drugs for treating high blood pressure.

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Recent Applications

Preparations derived from the root of *Rauvolfia serpentina* have recently been admitted in American and European clinical medicine as hypotensive and hypnotic drugs. In addition to lowering blood pressure quite efficiently, apparently without dangerous side-effects, habit formation, withdrawal symptoms or contraindication, these drugs have a sedative or tranquilizing action, said to result from a depressing effect on the hypothalamus. In advanced cases of hypertension they are valuable adjuvants to other agents, notably hydrazinophthalazine or Veratrum. The pure crystalline extract was marketed in November, 1953, by Ciba Pharmaceutical Products under the commercial name Serpasil (Ciba). The crude drug is also in the American market, for instance, as Raudixin (Squibb) which contains the whole powdered root of *R. serpentina*. Raudixin tablets were placed on the market in May, 1953. Rauwiloid (Riker) is a purified extract containing a mixture of principles. Serpina, manufactured by the Himalaya Drug Company in Bombay, has been sold in India for a comparatively long time. Experiments with the preparation were described by Bhatia and by Kapur in 1942. The active principle of Serpasil is a tranquilizer-antihypertensive alkaloid bearing the chemical name " reserpine ".

Early History

R. serpentina has an ancient history. It is said to appear in Sanskrit as an Ayurvedic medicine named Sarpagandha and Chandrá. Chandrá means moon and refers to the use of the plant in the " moon's disease " or lunacy; Sarpagandha, snake's smell or repellent, refers to the use as an antidote for snake-bite. Rheede in 1686 probably mentioned this species, at least in part, under the name Tsjovanna (or Sjouanna) Amel-Podi; he noted the use of the root against snake-bite and the sting of scorpions. Kaempfer in 1712 described the plant and its curative properties under the name Radix Mungo. Burman in 1737 applied the term Lignum Colubrinum to it. Linnaeus in Materia Medica, 1749, used the pharmacopoeic appellation Serpentini Lignum. Rumphius named the plant Radix Mustelae, in reference to the legend that the mongoose has recourse to it when bitten by a poisonous snake; he stated that the species came to his notice in 1693. Various other curative properties were early attributed to the plant, and it has accordingly been regarded as

a febrifuge, tonic, stomachic, sedative, soporific, eclampsia relief, cough-sedative, diuretic, purgative and anthelmintic. Trimen noted its use against hydrophobia. Dymock (1879) stated that in Bombay most of the laborers who came from southern Koncan kept a small supply of the root which they valued as a remedy in dysentery and other painful affections of the intestines. Roxburgh reported that it was administered to promote delivery in child-birth; Wight added that it was supposed to act on the uterine system somewhat in the manner of Ergot; Khory stated the root was said to cause abortion if given to pregnant women. Rama Rao described the " whole plant dried in shade, powdered and given in honey as a remedy in rheumatism, all poisons, insanity, epilepsy, fits and eczema ". " The juice of the fresh leaves has been mentioned for the treatment of corneal opacities " (Kapur). Dalzell and Gibson reported the plant used " to poison tigers ". It will be noticed that many of the empirical uses have a common denominator, the proven sedative or relaxing efficacy of the drug; reports of other presumed properties may have stemmed from a mistaken identity of the plant.

Modern Use in India

Before its introduction into occidental medicine, the dried root had already been on the market in India for about 20 years. One manufacturing firm alone claimed to have sold over 50 million tablets of the dried root. Sen and Bose in 1931 reported the drug valuable and safe in the treatment of high blood-pressure, " almost to a precision not found possible with any other drug, Eastern or Western ". They found it effective in insanity with violent maniacal symptoms. Deb in 1943 stated that *R. serpentina* checked psychotic excitability more effectively than any of the barbiturate group of drugs. The Indian Pharmacopoeial List in 1946 described the products Extractum Rauwolfiae Liquidum, Extractum Rauwolfiae Siccum and Tinctura Rauwolfiae. In 1949 Vakil concluded that after extensive trials of various hypotensive remedies in several thousand cases of hypertension, in both private and hospital practice during the previous ten years, he found *R. serpentina* to be the most consistently successful drug, meriting a definite place in medicine; it lowered both systolic and diastolic blood-pressure, and it was nontoxic, with only mild side-effects. In reply to a questionnaire that Vakil issued to 50 physicians all over India, 46 voted for *R. serpentina* as the best hypotensive agent in their experience.

Botany

R. serpentina is a member of the Apocynaceae, a family notable for its many biologically active principles. The species is widely distributed in tropical India, Ceylon and Java.

Synonymy. *Rauvolfia serpentina* (L.) Benth. ex Kurz, For. Fl. Br. Burm. 2: 171. 1877. (Spelled " *Rauwolfia serpentinum* ".)

? " *Clematitis indica foliis perficae, fructu periclymeni* " Bauhin, Pinax 301. 1671.

" *Tsjovanna-Amel-Podi* " & " *Sjouanna-Amelpodi* " Rheed., Hort. Malab. 6: 81. t. 47. 1686.—pro parte?

" *Radix Mungo* " Kaempf., Amoenit. Exot., fasc. 3: 573. 1712.

" *Ligustrum foliis ad singula intermedia ternis* " Burm., Thes. Zeyl. 141. t. 64. 1737.

" *Ophioxylon foliis quaternis* " L., Fl. Zeyl., ed. 1, 188. 1747. (Description erroneous; corrected under Restituenda, p. 239.)

Ophioxylon serpentinum L., Sp. Pl. 1043. 1753.

" *Radix Mustelae* ", " *Raiz de Mongo Alba* ", & " *Raiz de Mongo Rubra* "

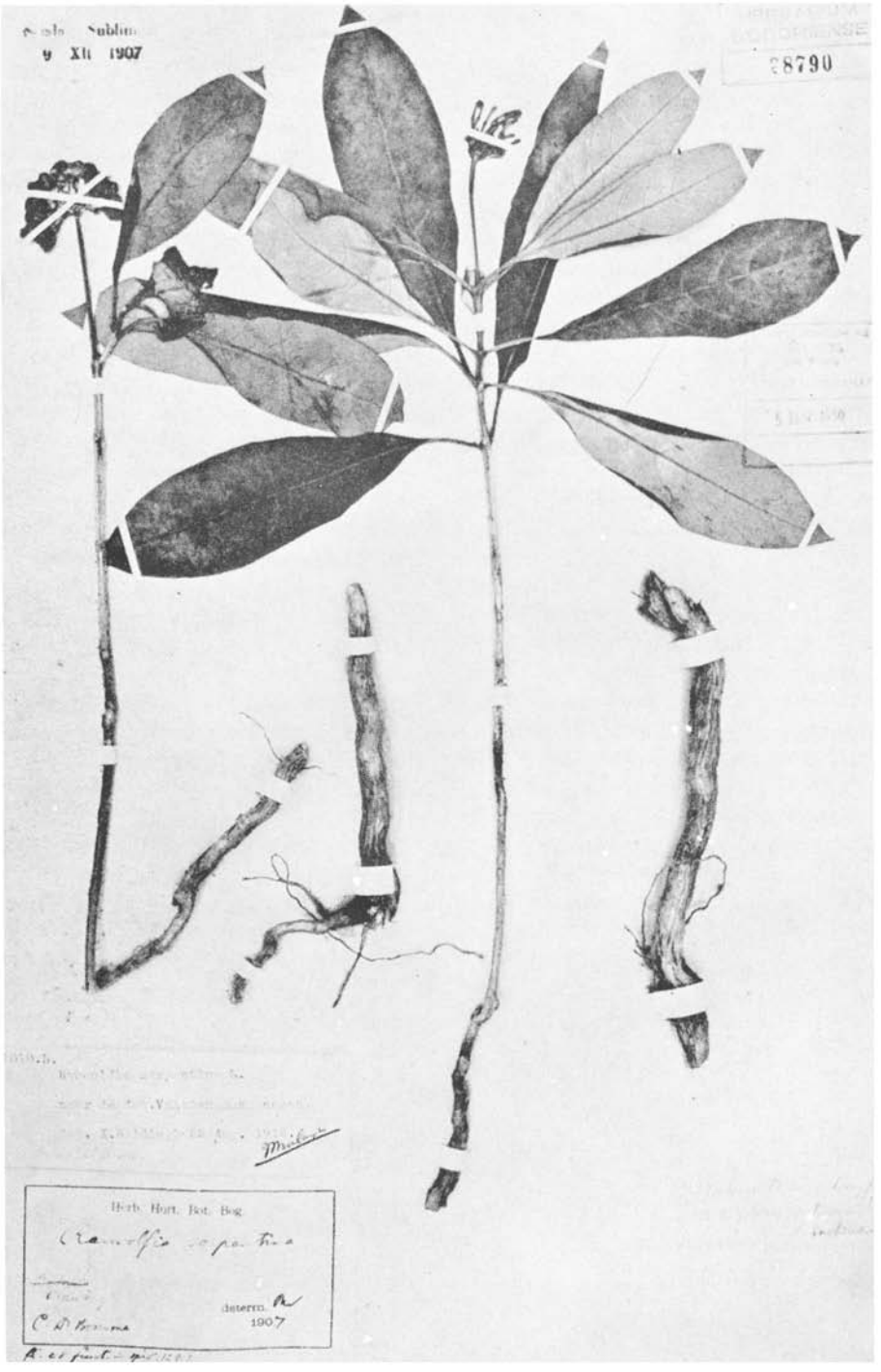

FIG. 1. *R. serpentina*, collected by Boorsma in Krawang, Java, in or shortly before 1907. Flowering and fruiting plants, including roots. The stems are 22 and 23 cm. long; the flowers are not fully expanded. (*Photo by courtesy of The New York Botanical Garden*).

Rumph., Herb. Amb. 6 Auctuarium (7): 29, 30. t. 14. 1755.

Ophioxylum trifoliatum Gaertn., Fruct. 2: 129. t. 109. 1791.

Ophioxylum album Gaertn., Fruct. 2: 129. 1791.

Ophioxylon Salutiferum Salisb., Prod. Stirp. 146. 1796.—superfluous name.

Tabernaemontana cylindrica Wall., Cat. 4451. 1830.—nom. nud. (Fide J. D. Hook., Fl. Brit. Ind.)

? *Ophioxylon Belgaumense* Wight, Ic. Pl. Orient. 4(2): 2. 1848.

Ophioxylon obversum Miguel, Fl. Ind. Bot. 2: 405. 1856.

Rauwolfia trifoliata (Gaertn.) Baill., Hist. Pl. 10: 171. 1891.

Rauwolfia obversa (Miquel) Baill., Hist. Pl. 10: 171. 1891.—Non Koord., 1901, as to description.

Description. Erect evergreen subshrub, 0.2–0.6 (–1) m. tall, glabrous, lactescent. Root bitter, its main axis vertical, single (rarely branched), tapering to base, up to 20 (–40) cm. long, 1–2 cm. thick, rimose, greyish rusty to brown. Rhizome resembling the root (fide Wallis and Rohatgi). Stem usually unbranched, slender; bark pale. Leaves usually more crowded towards upper part of stem, mostly 3-whorled, or a few leaves occasionally opposite or even alternate (leaves described as varying from opposite to 3–5-whorled); petiole 5–15 (–20) mm. long, glandular at axil; blade membraneous, green above, pale beneath, oblanceolate or obovate, sometimes lanceolate, 7–16 cm. long, 3–9 cm. broad, acuminate and finely acute, varying to blunt or evenly rounded at apex, tapering at base, the lateral nerves arcuate-ascending; 7–15 pairs, widely spaced, the principal ones mostly 1–1.5 cm. apart near middle of blade; fainter veins present between the principal lateral nerves. Inflorescence terminal or sometimes axillary, usually in dense crowded many-flowered cymes, forming a hemispheric head at the end of the peduncle; axis 0.5–1.5 cm. long; peduncle usually long and unbranched, sometimes sparsely branched, 5–9 (–13) cm. long; bracts minute, subulate from a triangular base; pedicels very short. Calyx-lobes esquamulose, almost free, deltoid to lanceolate, 1.3–3 mm. long, acute at apex, often with 1 or 2 minute teeth on margin near base. Corolla pink or white, salverform; tube 11–16 mm. long, slightly swollen at location of anthers slightly above middle, glabrous outside, pilose inside from about middle to orifice, lobes ovate-orbicular, rounded at apex, 1.5–3.5 mm. long, glabrous, convolute in bud with left margin overlapping. Stamens free, inserted well below orifice of tube, 3–5 mm. from apex; filaments very short; anthers oblong, 1.3–1.4 mm. long, apical mucro short if present, thecae rounded at base, dehiscent their full length. Disk subtending and partly cloaking the ovary, cylindric, 0.6–0.8 mm. long, truncate or lightly undulate at margin. Ovary about 1.2 mm. long, truncate, rounded or slightly concave at apex, narrowed to a stipe-like base, glabrous; carpels united at base to about length of disk; ovules suspended, two in each cell. Style about 8 mm. long; clavuncle short-cylindric, about 1 mm. long, membraneous tunicate at base, fringe-indusiate at apex; stigma of 2 minute apiculi. Drupes double (sometimes single by abortion), united about half way, oval, slightly flattened, 5–6.5 mm. long, 4.5–5 mm. broad; apices blunt, divergent so that the sinus makes an open V; flesh thin; endocarp osseous, lightly rugose; disk remaining as a thin collar at base of fruit. Seed single in each carpel, oval, flattened, about 6 mm. long; endocarp copious, soft; embryo erect; cotyledons aplanate, broadly oval, about 2 mm. long, 1.8 mm. broad; radicle cylindric, about 2 mm. long. An herbarium specimen (Herb. Hort. Bog. 6597, Rembang, Java) of a plant with abnormal corollas was examined: some of the corolla-lobes narrowly spatulate-lanceo-

late, longer than corolla-tube, up to 7 mm. long, pilose inside near base; anthers more or less abortive; ovary tapering at apex; disk low.

Type of the Species. Hermann's Ceylon collection deposited in the British Museum. Hermann collected mostly in the neighborhood of Colombo. Henry Trimen studied the Hermann collection and verified the type (Jour. Linn. Soc. **24**: 153. 1887). In Species Plantarum, Linnaeus cited Burman and Bauhin, besides his earlier Flora Zeylanica.

Distribution (mostly from literature). India, Ceylon, Andaman Islands, Burma, Siam, Java, Sumatra. Sub-Himalayan Pakistan and the Indian Union throughout where the habitat permits, in a variety of soils, in grassy, usually damp or shady places, ascending to over 1200 meters in the Khasia Mts.; the upper Gangetic Plains, Dehra Dun, Siwalik Range and in the Sub-Himalayan tracts of Rohilkhand, N. Oudh and Gorakhpur District westward to Sirhind along the base of the Punjab Himalaya, and eastward to Sikkim, Assam and N. and C. Bengal, and from Bombay through C. and S. India to Travancore; common in the Terai and Lower Hills up to 600 meters in Northern Bengal, common in the Koncans, Bombay Presidency; W. Ghats in Madras, all districts, moist forest undergrowth from low level up to about 1000 m. Throughout Ceylon, common in shady places in grass in moist regions up to 600 meters, banks of rivers, paddy fields. Burma, " very frequent in the mixed and open, especially in the savannah forests, all over Pegu and Martaban down to Tenasserim " (Kurz). Siam, " Pahombuk, Muang Fang, 1000 m. et Doi Intanon, 1700 m. (ex Hosseus) " (Craib). Java,[1] scattered throughout to an altitude of 650 meters or higher; residencies Batavia, Besoeki, Cheribon, Djapara, Kediri, Madioen, Pekalongan, Pasoeroean, Preanger, Rembang, Semarang. Amboina, where introduced from Java, according to Rumphius' observation in 1693; not represented in the Amboina collection (Merrill). Sumatra, fide Kaempfer. Wight stated that the plant is one of great beauty and much cultivated as an ornament.

Vernacular Names. INDIA: Chandrá (Bengali), Ch'hota-chand (Hindi), Chivan-amelpodi or Covannamiloori (Tamil), Dhannerna or Dhan-barua (Oriya), Pálalganni or Pátala-gandi (Telegu). CEYLON: Acawerya. JAVA: Akar Tikoes, Poelé (or Poeleh) Pandak.

The following is an alphabetical list of all the vernacular names encountered for the species:

Acawerya
Aika-wairey
Akar-tikoes (Accarticos)
Bongmaiza
Bhudra
Chandrá
Chandrika
Chota-Chand
Chota-Chard
Chundrika
Chundrushoora
Churmuhuntree
Chivan-amelpodi
Chuvanna-avilpori
Covannamiloori
Dhannerna
Dhan-barua
Eiya-kunda
Ekawerya
Garudpathal
Hadki
Harkai
Harkaya
Ichneumon plant
Karai
Karavi
Karuvee
Kshermakshi
Makeshwar Chakrika
Makeshwar Churna
Matavi-aloos
Moogsavel
Nogliever
Nundunee
Pagal-ka-dawa
Pálalganni
Pátala-agandhi
Pátala-gandi
Pátala Garuda
Pátalgarur
Poeheh Pandak
Poelé Pandak (Pule Pandac)
Pushoomehunukarika
Radix Mungo
Radix Mustelae
Raiz de Mongo Alba
Raiz de Mongo Rubra
Rametul
Ratekaweriya
Ratu Eka-weirya
Sapasan
Sarpagandha
Sjouanna-Amelpodi
Sung
Suvapaval-poriya
Tsjovanna Amelpodi
Talona
Vasoopooshpa
Vasura

" Makeshwar Chakrika " and " M. Churna " were the names used by Maka-

[1] The notes presented by Koorders (Exkursionsflora von Java **3**: 74. 1912) refer to *R. perakensis* (or *R. verticillata*) and *R. serpentina* together, for Koorders, like some other botanists, did not distinguish the two species.

mahopadhyaya Gananath Sen for the pill or tablet preparation and the powdered drug. " Pagal-ka-dawa " was the name of the drug used as an insanity specific in India. Some of the names listed above may be due to mistaken identity. Also, as is often the case, the same vernacular name may be applied to other species. For example, " Poelé Pandak " has been applied to *Plumbago indica* L. and to other species, according to Heyne. Sen and Bose pointed out that " Sarpagandha " has been employed in Ayurvedic literature to mean " Rasna ", which cannot be identified with *R. serpentina;* " Chandrá " and " Chandrika " have been applied to five or six drugs, none of them identified as *R. serpentina.*

Field Observations and Culture [2]. The flowers are reported red or white, or whitish tinted with shades of red. The Jacquin illustration shows red corolla-tube and white limb. Drupes purplish-black when ripe (" lateritio-rubra " Gaertner; " glossy crimson " Kurz). Nucleus white, oily, vapid subsweet (Kaempfer). Pedicels and calyces bright red (calyx green, somewhat red at the tips of the lobes, according to Wendland). Cooke quotes W. Jones: " Few shrubs are more elegant, especially when the vivid carmine of the perianth is contrasted not only with the milk white corolla, but with the rich green berries which at the same time embellish the fascicle; the mature berries are black and their pulp light-purple ". The plant flowers from April to July (Nov., Dec., fide Duthie) and fruits from July to September, but flowers and fruits occasionally may be found throughout the year.

In cultivation under glass the plant does not seem to bear fruits. Jacquin stated that he examined flowers several years and found that they were early deciduous, and that no fruits were formed. Wendland observed the plant blooming for six years, but not setting fruit. Sims noted that the cultivated plant requires heat but does not like the sun.

A plant raised from seed obtained from Calcutta in 1901 was in the Conservatory of The New York Botanical Garden, and a flowering specimen was collected in March, 1906. At the present time there is no living plant of *R. serpentina* either at New York or at the U. S. Department of Agriculture, Beltsville, Maryland. E. A. Menninger maintained in Florida a nursery stock of the species as an ornamental plant, but his entire stock was sold almost overnight last year when there began to be great interest in the drug.

J. Douglas, Curator, Botanical Garden of Indonesia, is intimately acquainted with the plant in the field. He communicates that the plant in Java reaches maturity and maximum height (about 50 cm.) in about two years, and that afterwards the root increases in size. The plant fruits readily after flowering Experiments conducted in West Java demonstrate that stem-cuttings root, although not easily. Propagation by seed was difficult; 30 percent germination was obtained. The plant did not thrive well in the very moist climate of West Java (rainfall about 4000 mm. a year).

D. M. A. Jayaweera, Superintendent Royal Botanic Gardens, Peradeniya Ceylon, reports that *R. serpentina* is common in Ceylon, and that the quickest way of propagating it is by division of the root-stock. One hundred percent of divided root-stocks established in two weeks; the same percentage of terminal cuttings sprouted roots in four weeks in sandy beds. Seeds took two or three months to germinate, as they are protected by a thick coat. Boiling or burning may encourage early germination.

[2] Roxburgh stated that the plant in rich soil is a large climbing or twining shrub; in poor soil, small and erect. The error " large climbing or twining shrub ", has been repeated by Wallis and Rohatgi, Watt, etc., even as late as 1952 (by Trease).

The Root. Dymock stated that the odor of the fresh root is acrid, and that the wood is remarkably starchy. He presented a short description of the root and its anatomy. Wallis and Rohatgi wrote that the rhizomes closely resemble the roots but are less uniform in diameter; they differ histologically in certain respects only, best distinguished by the very small diameter of the central pith in the rhizome exhibited in transverse sections. They found no typical laticiferous tubes in the roots and rhizomes. Youngken stated that the resin cells may occur in the cortex, phloem and xylem, and are especially abundant in the Dehra Dun variety. He described the microscopic structure of the root of commerce, huge amounts of which, he noted, have been imported by manufacturing pharmaceutical firms in the United States.

According to Dymock (1879), the root formerly was not an article of commerce. The Indian Pharmacopoeial List of 1946 specified that the root of *Rauvolfia* be collected from three- to four-year plants in autumn, and that the material contain not more than two percent of organic admixture and not less than 0.8 percent of total alkaloids. Chakravarty et al. found that the dried root contains about one percent of total alkaloids; Gupta and Kahali detected 1.21–1.36 percent.

Illustrations. Excellent colored illustrations of the flowering plant are presented by Jacquin, Sims and Trattinick; others by Wendland (flower analysis in color), Wight (stem with leaves, flowers and fruits; flower and fruit analyses, embryo), Gaertner (fruit analysis), Burman (stem with leaves and fruits), Lamarck (stem with leaves, flowers and fruits; fruit analysis), Rumphius and Rheede (rough sketches; stem with leaves, flowers and fruits; root). A colored illustration of undesignated origin (stem with leaves, flowers and fruits) is being distributed by S. W. Akkarappatty and Co., Wholesale Drugs and Herbs Dealers, Trichur, S. India. A photo is shown by Youngken (stem with leaves and inflorescence; cross-segment of root). Wallis and Rohatgi offer extensive anatomical drawings of the root and rhizome; their reproduction of the flowering plant is taken from Wight. Pool presents a microscopic view of the epidermis and other anatomical features, also the root and a rough sketch of the stem with leaves, flowers and fruits. Index Londinensis also lists the following (not seen): Basu (Ind. Med. Pl., t. 602. 1918), Greshoff (Nutt. Pl., t. 46. 1900), Plenck (Ic. Pl. Med., 8 t. 732. 1812). Miquel observed that the illustrations in Burman and Wight are not of the species, the former probably being referable to *Ophioxylon ceylanicum* Wight. On the contrary, both drawings show connate drupes and a crowded inflorescence, and are in general fairly representative of *R. serpentina*. The drawing of *Ophioxylon ceylanicum* shows separate drupes and a relatively loose inflorescence; it is good for *R. densiflora*.

Discussion of Synonymy. The original spelling of the generic name by Linnaeus in Genera Plantarum in 1737 and subsequently to the seventh edition in 1767 was *Rauvolfia*. This orthographic variation was also used in the first edition of his Species Plantarum and subsequently to the seventh edition. In the eighth edition, 1778, the spelling was changed to *Rauwolfia*, which is the commonly accepted form. In strict usage and in compliance with the International Code of Botanical Nomenclature, the name should be spelled *Rauvolfia*.

In the foregoing synonymy under *R. serpentina*, there cannot be any assurance regarding identity of the plant referred to by Bauhin. The same doubt holds for other early works. Rheede's description of connate drupes, corolla extended near the middle, and bitter roots identifies his species with some greater confidence. His illustration,

however, depicted opposite, not ternate, leaves, and he described the size of the plant to reach the height of a man, which is much too tall for *R. serpentina*. On the other hand, Kaempfer's description can hardly be questioned: size of the plant about one foot, the drupes coalesced at the base and about the size of coriander fruits, the flowers globular-congested, the simple bitter root about a span long and the thickness of a finger. Burman's illustration adequately characterizes the species.

Rumphius noted two color forms of Radix Mustelae. He observed that they did not differ in leaf, flower or fruit, except that Radiz de Mongo Rubra had firmer leaves, reddish beneath, mostly ternate, reddish flowers, and roots not so bitter. He aptly compared the fruit to the likeness of two pepper grains pressed against each other. The corolla was depicted inflated near the middle, and the fruits apically rounded as in *R. serpentina* instead of pointed as in *R. verticillata*. Burman, in Flora Indica (pp. 42 & 218. 1768), placed Radix Mustelae of Rumphius in the synonymy of both *Ophiorrhiza Mungos* L. and *Ophioxylon serpentinum*. Rumphius' characterization of the seed and his assertion that the plant is lactescent precludes *Ophiorrhiza* (Rubiaceae).

Linnaeus' description under n. 398 in Flora Zeylanica is altogether incorrect for the species (corolla-limb with a cylindric nectarium as in *Narcissus*, calyx bifid, stamens two). The error was rectified under his Restituenda in the same work. Linnaeus cited the Acawerya of Hermann's catalogue, besides previous literature, Burman, Bauhin, and " Garc. Arom. 163 ".

Gaertner illustrated connate drupes for his *Ophioxylum trifoliatum*. The species is thus best referred to *R. serpentina*. *Ophioxylum album* was based on Rumphius' illustration of Raiz de Mongo Alba. It is sometimes united with *Ophioxylon majus* Hasskarl. The latter is most probably the Java representative of *R. verticillata* (*R. perakensis*), a shrub usually over four feet tall and with free drupes. Rumphius stated that Raiz de Mongo Alba did not exceed two feet in height. The sketch showed opposite, not whorled, leaves, and this was noted by Gaertner as a point of difference from his *O. trifoliatum*. The sketch was very rough, and the leaf arrangement is best regarded as inaccurate.

Hooker wrote about *Ophioxylon Belgaumense:* " I find no specimen of this in Wight's Herbarium; but for the calyx it seems identical with *R. serpentina* ".

The type of *Ophioxylon obversum* Miquel, an Horsfield flowering specimen from Blambangan, Java, compares very well with *R. serpentina*. Miquel incorrectly described the cymes and calyces of *R. serpentina* as pubescent, indicating that he did not clearly understand the species. Koorders, unaware that Baillon had already effected the combination, published *Rauwolfia obversa* (Nat. Tidsschr. Ned. Ind. **60**: 243. 1901). His basonym was Miquel's name, but his description was of *R. verticillata*. He observed that the long fruit of his Tenger collection made separation of the species from *R. serpentina* recommendable. He annotated the Tenger collection 38156β: " = R. obversum Miq. = Horsf. Apocy. n. 22! in herb. Kew ". Later, in 1912, Koorders altered his concept and referred both the Tenger species and Miquel's *Ophioxylon obversum* to *R. serpentina*, " sensu latissimo ", noting the latter to be a very polymorphic species. Thus by falling into a double error he arrived at the correct conclusion regarding the synonymy of *R. obversa*.

Hunteria sundana Miquel is placed in the synonymy of *R. serpentina* by Heyne. Miquel, himself, indicated the species to possess the character of *Ophioxylon*. However, the original placement of it in *Hunteria*, a genus with free

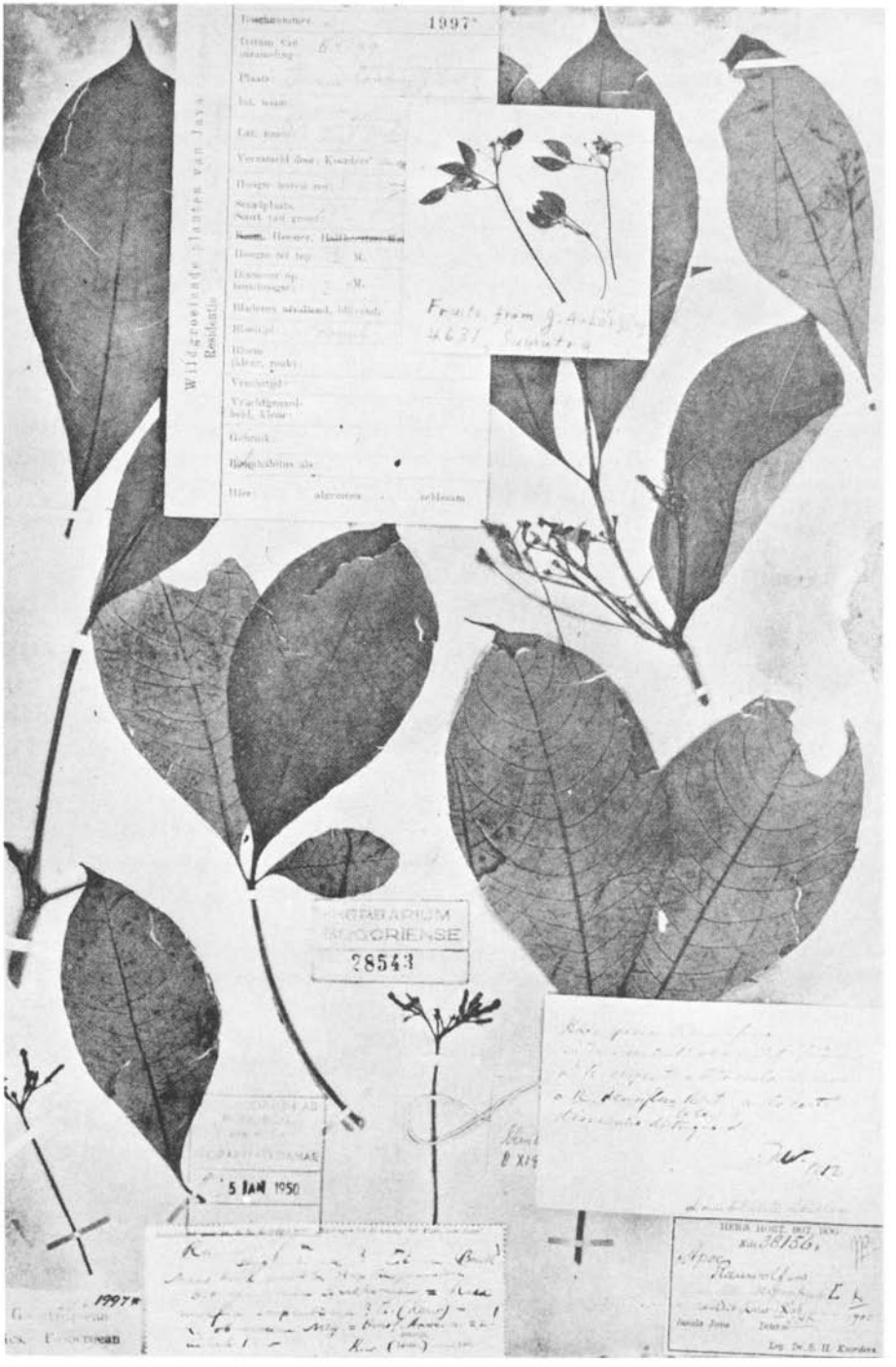

FIG. 2. *R. perakensis* (a variety or form of *R. verticillata*), collected by Koorders (38156B) on Mt. Ardjoeno, Pasoeroean, Java, 8 Nov. 1899. This species has been mistaken for *R. serpentina*, but the loose habit of its inflorescence distinguishes it. The fruits are from a specimen collected by Lörzing in Sumatra. They are free and pointed, whereas those of *R. serpentina* are half united and blunt. (*Photo by courtesy of The New York Botanical Garden*).

fruits, and the description of the fruits as ellipsoid subsessile would suggest a species other than *R. serpentina*. Heyne did not distinguish *R. serpentina* from *R. verticillata*.

Species Related to *R. serpentina*. *Rauvolfia* is a large genus, comprising about 110 species according to Pichon. This number probably will be greatly reduced when the synonymy is known. It is distributed in the tropics of nearly the whole world: Middle and South America, Africa, India, Malaya, China and Japan. The genus apparently is absent from Australia and New Zealand. The most numerous species are in America and Africa. The species vary in size from dwarfs with annual shoots up to 15 cm. high (*R. nana* E. A. Bruce) to rather large trees about 25 meters tall and 30 cm. in diameter (*R. caffra* Sond.).

Pichon recognizes 14 sections in the genus. In section *Ophioxylon* (characterized by the more or less coalescent drupes), where he placed *R. serpentina*, he has (as doubtful) one other species only, *R. membranifolia* Kerr, of which he studied the fruits. The drupes of *R. micrantha* Hook. f. are connate to the middle, as described by Hooker. The sinus at the apex of the double-fruit of *R. micrantha* forms a much more open angle than that in *R. serpentina*, so presenting a broadly emarginate to truncate apex.

The drupes of *R. densiflora* (Wall.) Benth. ex Hook. f. are free, larger and more pointed at the apex than those of *R. serpentina*. The inflorescence is looser, notwithstanding the specific appellation " densiflora ". The stamens are located at the summit of the tube, the corolla-lobes are longer. *R. verticillata* has the fruit and inflorescence character of *R. densiflora*. Its stamens, however, like those of *R. serpentina*, are situated decidedly below the orifice of the corolla-tube.

R. perakensis King and Gamble, which has been called Poeleh-padak in Java and confused with *R. serpentina*, is infraspecifically, if at all, distinct from the Chinese *R. verticillata* (Lour.) Baill. (= *R. chinensis* (Hance) Hemsl.). It has also erroneously been called *R. densiflora* in Java. *R. majus* (Hassk.) Nichols. may also be the same as *R. verticillata*.

Under his section Dissolena, Pichon indicated that he studied *R. verticillata*, *R. chinensis*, *R. perakensis* and *R. majus*. He listed these species separately, as though distinct; but the first two are synonymous, and the remaining two are only varietally, if at all, distinct from *R. verticillata*.

A study of the relatives of *R. serpentina* would require examination of the following additional species: *R. peguana* Hook. f. (= probably a form of *R. verticillata*), *R. microcarpa* Hook. f., *R. Beddomei* Hook. f., *R. membranifolia* Kerr, and *R. ophiorrhizoides* (Kurz) Kerr (= probably a form of *R. verticillata*). Not a single specimen of these seven species is available in the principal American herbaria (a specimen named *R. ophiorrhizoides* is at the Arnold Arboretum, but its determination is doubtful). The specimens of *R. Loheri* Merrill and *R. membranacea* Merrill are poor; *R. rivularis* Merrill is represented by a single flowering specimen. Stapf described *R. serpentina* var. *gracilis* from Borneo, but this variety is better referred to *R. verticillata*. For a complete survey two other names should also be investigated, *Ophioxylon Belgaumense* Wight and *Hunteria sundana* Miguel.

Chemistry and Pharmacology

Other Rauvolfia Species. Eight or nine species of *Rouvolfia* have been investigated chemically. *R. canescens* L. and *R. heterophylla* Roem. and Schult. (southern Mexico and the West Indies to northern South America) are considered by Woodson as varieties of a single

species, *R. hirsuta* Jacq. and *R. hirsuta* var. *glabra* (Muell. Arg.) Woods. Chemical literature on five African species has been seen: *R. caffra* Sond. (Belgian Congo, Transvaal), *R. mombasiana* Stapf (East Africa, Kenya to Mozabique), *R. natalensis* Sond. (Nyasaland, Natal), *R. vomitoria* Afzel (West Africa, Belgian Congo, Tanganyika), and *R. obscura* (Belgian Congo).

Adulterants. Youngken states that the roots of *R. perakensis, R. densiflora,* and especially of *R. canescens* have been found as substitutes and adulterants in commercial lots labeled "Rauwolfia Serpentina Root". Mookerjee also revealed that the roots of *R. canescens* are sometimes used to adulterate those of *R. serpentina. R. canescens* is American but sometimes occurs in areas of India where *R. serpentina* abounds. The species is not generally treated in the floras of India. Haines (1922) states: "Orissa, near Cuttack, etc., apparently an escape from cultivation!"; Gamble (1923): "found in gardens and sometimes run wild in the neighborhood of Madras". However, Mookerjee (1941) wrote that the species is locally known as "Barachándá" and that it inhabits the moist and hot regions of India.

Chemistry of *R. serpentina*. The chemical, pharmacological and clinical literature on *R. serpentina* or its alkaloids is extensive, and only partial mention of it can be made here. Reserpine was isolated for the first time by Müller, Schlittler and Bein in 1952. The chemistry of this alkaloid was thoroughly studied in 1953 by Dorfman, Huebner, MacPhillamy, Schlittler and André (Research Laboratories of Ciba Pharmaceutical Products, Inc., Summit, New Jersey); Furlenmeier, Lucas, MacPhillamy, Müller and Schlittler; Klohs, Draper, Keller and Petracek (Riker Laboratories, Inc., Los Angeles, Calif.); Neuss, Boaz and Forbes (Lilly Research Laboratories, Indianapolis, Ind.); Stoll and Hofmann. Chatterjee and Bose announced the new alkaloid rauwolfinine in 1951; Rose further studied this compound in 1952. Stoll and Hofmann isolated the new alkaloid sarpagine in 1953. Bodendorf et al. conducted pharmacological tests with the alkaloid raupine in 1953. The alkaloid serpentine was investigated by Schlittler and Schwarz in 1950.

Wilkins and Judson (1953) confirmed the distinct pharmaceutical excellency of *Rauvolfia;* they found that the drug given in conjunction with other hypotensives "appeared to exert a remarkable additive, if not synergistic, hypotensive effect". The side effects were few and none serious, they concluded, those worthy of emphasis being bradycardia, nasal congestion, sedation and a tendency to gain weight. In a paper summarizing the drugs used orally in the current treatment of hypertension, Wilkins (Nov. 1953) concluded that *Rauvolfia* is "particularly useful alone for relieving young, labile, psychoneurotic hypertensive patients with tachycardia". Other physiological or pharmacological studies have been conducted by Chakravarty and Chaudhuri (1951), Roy (1950), Mazumdar and Mukherji (1950), Bhatia (1942), Kapur (1942), Paranjpe (1942), Raymond-Hamet (1936–1949), and also Chopra, Gupta, Dutt, van Itallie and collaborators.

Siddiqui found chemical differences in the roots of *R. serpentina* collected in the hot swampy districts of Bihar and in the climatically milder Dehra Dun Valley; Bhatia and Kapur detected pharmacological differences in the roots from the two localities. In a preliminary investigation of two known and four unknown varieties from several sources, Nelson and Schlagel found the Dehra Dun variety showing the greatest activity. A method of assay of the roots was elaborated by Mahadeva Lal Schroff and Rattan Lal Bhatia. A micromethod for

determination of the alkaloids was presented by Bakshi.

In 1888 Wefers Bettink investigated the chemistry and pharmacology of the roots of Poeleh Padak obtained from a druggist in Cheribon. He identified the plant as *R. serpentina,* but did not see the flowers to check the identification. The taste of the root he studied was sharp, like that of horse-radish, not bitter as described by Rumphius or as in the Dymock root. Extracts killed earthworms quickly. He called the principle " ophioxyline ".

The Merck Index (6th Ed., 1952) states that ophioxyline is obtained from the roots of *R. serpentina;* it lists Wefers Bettink and two other old references, Greshoff (1890) and Warden and Bose (1892). As previously indicated, Poeleh Padak in Java has been applied to other species besides *R. serpentina.* It is doubtful that Wefers Bettink correctly identified the material he studied. Neither of the two remaining citations given in the Merck Index supports the presence of ophioxyline in *R. serpentina.* Greshoff indicated the identity of ophioxyline with plumbagine and suggested that *R. serpentina* had been confused with *Plumbago rosea* L. Both species, he pointed out, bear the same name, " Poeleh Pandak ", in Java. Warden and Bose did not mention ophioxyline but merely announced the extraction of an alkaloid which they provisionally termed " pseudobrucine ".

Additional alkaloids reported for the species are: ajmaline, ajmalinine, ajmalicine, isoajmaline, isorauwolfine (possibly identical with isoajmaline), neoajmaline, rauwolfine (possibly identical with ajmaline), rauwolscine[3] serpentinine. Wehmer also lists serposterine.

[3] Rauwolscine was listed for *R. serpentina* by Mazumdar and Mukherji in 1950. This alkaloid was first isolated from *R. canescens* by Mookerjee in 1941.

The Squibb Institute for Medical Research has issued a typewritten four-page list of 46 references dealing with the chemistry and pharmacology of *R. serpentina,* embracing the years 1931 to 1953. Two pages of additional references, containing 18 entries, were included in December, 1953. A conference on " Reserpine (Serpasil) and other alkaloids of Rauwolfia serpentina: chemistry, pharmacology and clinical applications ", sponsored by The New York Academy of Sciences, was held in New York City on February 5, 1954. An annal with this title, comprising about 200 pages, is to be published by the Academy in 1954.

The Drug in Commerce. Serpasil is not yet commercially available in Great Britain, according to a private communication (Dec. 1953) from W. Gwynne Thomas, Pharmacy Department of the University of Manchester. Mr. Thomas wrote further that " Messrs. Ciba Laboratories Ltd. have a small stock of experimental material at their laboratories in Horshan, Sussex, which is available to persons wishing to investigate the properties of the substance, or to members of the medical profession who wish to conduct clinical trials ". Products of *R. serpentina* have been marketed in Switzerland, Germany, and in this country.

A brochure prepared by Squibb summarizes the advantages of Raudixin. Some of the advantages given are: safety, mild brachycardia, sedation and laxation, symptomatic improvement, convenient oral dosage. Another example of commercial advertisement of the drug appears on the back covers of the 1953 June, July and August issues of the American Journal of Pharmacy, where Raudixin Tablets (Squibb) are stated to permit an improved approach to ideal hypotensive therapy. It is asserted that the drug has a more stable hypotensive effect than other agents; critical adjust-

ment of dosage is unnecessary; and tolerance to the hypotensive effect has not been reported. In the September issue Squibb advertised that wide clinical experience to date still makes the whole crude root the preferred form of the drug. A brochure circulated by Ciba states that Serpasil, being a single pure crystalline alkaloid, yields predictable constant results and offers unvarying potency with accuracy in dosage in comparison with whole root therapy. Mazumdar and Mukherji (1950) pointed out that ajmaline and serpentinine raise the blood pressure; hence the total alkaloids of the root contain components which act antagonistically, raising as well as lowering the blood pressure.

Treatment in Standard Literature. As indicated in the 24th edition, 1947, of the Dispensatory of the United States, the drug is not yet official in the U. S. Pharmacopoeia, the Pharmacopoeia of Great Britain or the National Formulary. C. O. Lee's, The Official Preparations of Pharmacy (2nd Ed., 1953), does not contain *Rauvolfia,* nor does M. E. Howard's Modern Drug Encyclopedia and Therapeutic Index (5th Ed., 1952). The species has not yet been generally admitted in textbooks on pharmacognosy. It probably will be a standard item in the pharmacopoeias and pharmacognosy textbooks of the future.

The species is mentioned briefly in the 6th ed. (1952) of Trease's " A Text-book of Pharmacognosy ", but only in connection with the " Rauwolfia drug " long used in Indian medicine. Trease states that the alkaloids in *R. serpentina* do not appear to account for the sedative and hypnotic actions. He relied on Gupta et al. (1944, 1947) and possibly on Dutt et al. (1947) who claimed that the principle possessing these properties resides in the oleoresins; but Müller et al. in 1952 isolated the sedative alkaloid reserpine from the oleoresin fraction.

Summary

Rauvolfia serpentina, an ancient Indian medicine, is now ranked amongst the most valuable drugs for the treatment of high blood-pressure. It is particularly useful in mild hypertension or as an adjuvant in advanced cases. Until quite recently, it was neglected by the Western World, notwithstanding that careful investigation of the crude drug in India had consistently rendered a very high account of the plant. In 1952 the pure crystalline antihypertensive-tranquilizer alkaloid reserpine was isolated from the root.

R. serpentina has an Indo-Malaysian distribution. It is a subshrub with a congested inflorescence and half-connate drupes. Its botany is rather simple. There are only a few related plants likely to be confused with the species when adequate botanical material is examined. Sterile specimens may cause difficulty. It can hardly be entirely explained why *R. perakensis,* itself merely a variety or form of the Chinese *R. verticillata,* has been indiscriminately identified with *R. serpentina* in Java. The fruit character easily distinguishes the two.

Trial cultivation of *R. serpentina* is being made. Propagation by root-stock cuttings is successful. As there are strains of the species that differ in activity, particularly good strains should be sought for large-scale plantations.

The genus *Rauvolfia* is large and has a wide distribution in the tropics. Only a small percentage has been carefully investigated chemically and pharmaceutically. Numerous laboratory and clinical studies have been conducted with *R. serpentina,* and the literature in scientific journals is extensive. However, because of its only recent ascendency in Western medicine, it has been generally omitted from standard pharmacological books. In the future *R. serpentina* will

probably be accorded a definite place in pharmaceutical literature, in clinics and in tropical plantations of medicinal plants.

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Utilization Abstracts

Candlenut Oil. This oil, obtained by cold expression from the kernels of *Aleurites moluccana,* a generic relative of the tung tree, has been utilized commercially in Australia as a satisfactory alternative to linseed oil. While candlenut seeds contain 62 to 67% of oil as compared with only 36 to 40% in linseed, the residual cake of the former, after extraction of the oil, is toxic and must seek a commercial outlet as a fertilizer instead of as a cattle feed in competition with linseed oil cake. (W. D. Raymond and Miss. J. A. Squires, *Colonial Plant and Animal Products 3(3): 229. 1952–3*).

Cloves in Cigarettes. In Indonesia a type of cigarette manufactured and smoked only there and known as " kretek " is distinguished by its containing shredded cloves, or " tjenkeh ", an ingredient which causes a crackling effect during burning. Cloves imported from Zanzibar, instead of locally grown material, are used for this purpose, and when the Zanzibar clove harvest failed in 1952, about 200,000 workers in the Indonesian kretek industry became unemployed.

" Originally, this type of cigarette consisted of an outer wrapper of either dried maize leaf, dried banana leaf or dried palm leaf which was filled with a mixture of native shag tobacco and shredded cloves (10 parts of tobacco to 6 parts of cloves). The modern cigarette is machine-made and has the usual paper wrapper. The general method of adding the cloves as practised by the large cigarette manufacturers is to cut the cloves into 20 or 30 small pieces, but the smaller manufacturer grinds the cloves for mixing with the tobacco ". (*Colonial Plant and Animal Products 3(3): 252. 1952–3*).