CASTELA NICHOLSONI, HOOKER, SIMARUBACEAE. BOTANY, PHARMACOLOGY, AND THERAPY.*[1]

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These investigations, as far as planned for the time, were completed during the early part of 1923, but the laboratory notes and correspondence, inclusive of the drawings, as well as most of the text matter, were destroyed in the Berkeley fire of September 17th, 1923. These circumstances will account for the delay in submitting the report. Furthermore, much of the correspondence and pharmacologic laboratory data could not be repeated or duplicated and are here summarized largely from memory. The drawings by my daughter have been remade, but three excellent photographic productions showing the morphology of the leaves and stems of the drug plant, furnished by Mr. Crosbie (through the courtesy of H. Engelhardt) of the firm of Sharp and Dohme, intended as a contribution to the report, were also destroyed in the fire mentioned and could not be duplicated.

The interest in *Castela Nicholsoni*, known as *Chaparro amargosa* and as Mexican bitter bush or simply as bitter bush, and also goat bush, was awakened through the published articles by the Nixons of Texas, in which they report on its value in the treatment of amebic dysentery. The plant has long been known to the natives of Mexico who considered it almost infallible in the treatment of dysentery. It is known that the army of Zachary Taylor, during the Mexican war, acting on the reports of the Mexican Indians, also used this drug against dysentery, with great success. Putegnat reports a case of malaria which was treated successfully by an infusion of Chaparro. The Nixons of Gonzales, Texas, were, however, the first to give the drug serious attention and to try it out therapeutically in many cases of amebic dysentery.

Mr. Nixon of Honda, Texas, furnished 100 pounds of the crude drug (stems and leaves) of recent growth. The preliminary investigations with this material were begun in the laboratories of the School of Pharmacy of the University of Nebraska. Miss Naomi Zimmermann of the Department of Chemistry began the chemical investigation of the drug but soon abandoned the undertaking for other work. It was her opinion that the active constituent was glucosidal in nature. Mr. Bukey, of the School of Pharmacy, verified the work by Putegnat as to the chemical constituents present but his results cannot be given as his report was destroyed in the fire mentioned. Miss Gretchen Sprecher, a student in the School of Pharmacy of the University of Nebraska, made a comparative study of the toxicity of the purified (detannated and degummed) solid (dry) extract of Chaparro and of emetin hydrochloride, on frogs, and found that the latter was about 20 times more toxic than the former, results which were found to be approximately correct according to subsequent tests. The final investigations, as herein recorded, were carried out in the laboratories of the North Pacific College of Oregon, Portland. The report hereby follows.

Botany of *Castella Nicholsoni* Hook, Simarubaceae.—A genus of three or four known species mostly natives of the Antilles, one of which (namely the one herein

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described) is found on the coast of Texas and in northern Mexico. They grow in arid soils.

Flowers by abortion polygamo-dicœcious, small, solitary or somewhat fascicled in the axils of the leaves, subsessile, saffron colored. The calyx is small, four ovate to triangular sepals united at the base, deciduous. Petals four, oval, concave, much larger than the sepals, hypogynous, imbricate in estivation, deciduous. Stamens 8, alternate and opposite the petals into the base of a very short gynophore or hypogynous disk, filaments subulate, anthers cordate-ovate, fixed near the base, extrorse, two-celled, longitudinally dehiscent. Pistil wanting or abortive in the sterile flowers; in the fertile, seated on the very short gynophore, of four carpels united only at the axis; ovary deeply four-lobed, four-celled, the cells opposite the petals; styles distinct or united at the base, acute, revolute, stigmatose down the inner face. Ovule solitary and pendulous in each cell, anatropous.

Fruit of four distinct spreading substipitate drupes, or by abortion fewer; the rugose or pitted and compressed endocarp at length two-valved after the fleshy exocarp dries up. Seed solitary, conformed to the cell, obovate, pendulous, anatropous, with the micropyle a little produced, testa membranaceous. Embryo large in thin fleshy albumen. Cotyledons broad and flat, foliaceous, caulicle short, superior.

Low, very woody shrubs with sharply spinescent branches also bearing spines in the axils of the small, oblong-ovate, thick rigid, entire, alternate, subsessile leaves. The leaves are smooth shining above, silvery-canescent underneath, falling away easily on drying. Stipules none. Numerous trichomes; and stomata few on lower surface, wanting on upper surface. (See figures.)

Morphology and Histology.—The plant reveals some interesting morphological adaptations to soil and climate. It is a dry soil (arid) plant found in regions with a minimum of rainfall (annual precipitation of $^1/_2$ to $1^1/_2$ inches) but with a fairly high nocturnal atmospheric moisture. The leaves are small, comparatively few in number, and the photosynthetic processes take place largely in the chlorophyll-bearing parenchyma of the younger branches. The branches are provided with remarkable water pores, and the vascular conducting tissue of the woody center is associated with a water-storing tissue. Each water pore consists of two parts. The outer crater-like portion receives the water which condenses (in the night) upon the greatly thickened cuticle of the epidermis. This moisture condensation is due to the rapid loss of heat *via* the trichomes and the greatly thickened cuticle, as soon as the sun has set. The guard cells now allow the condensed moisture to pass into and completely fill the second chamber or reservoir. The younger branches, as well as the lower surface of the leaves, contain numerous rather long and twisted single-celled trichomes, which also have greatly thickened walls (the cell-lumen being almost completely occluded). The heat irradiation of the trichomes is further increased by the numerous minute warty prominences of the cuticle. The trichomes thus play an important part in the surface precipitation as well as holding or storing (temporarily) of the the night air moisture. As is known, the thalli of crustose lichens are hygroscopic, readily taking up atmosphere moisture, and no doubt the abundant deposit of these plants upon the older stems and branches assists in the precipitation of atmospheric moisture for the use of both symbionts. In other words, the lichen deposits of the older branches in a measure take the place of the water pores of the younger branches.

The comparatively small volume of water which the plant can accumulate and store during the night is again used during the day. The plant probably would not survive in a soil area of equal paucity of moisture precipitation and less atmospheric moisture. Thus it probably would not thrive in the more inland arid regions of Mexico, Arizona and New Mexico, where the cactus with its much more highly developed water storing tissue can tide over variably prolonged periods of little night moisture. Castela is remarkably adapted to the rather limited coastal areas of little or no rain and considerable night moisture. Whether or not this plant would thrive in the sandy, gravelly soil of those regions having a more abundant rainfall and also considerable night atmosphere moisture, as southern California, has not been determined. Nor are there any accurate data as to the temperature ranges of this plant. For the time being there need be no concern as to the supply. There is also considerable uncertainty as to the exact geographic range of *Castela Nicholsoni* and as to its morphologic variation in different geographic areas.

The woody nature of the plant, the extremely bitter taste, and the abundant thorns and needle-like branch termini, protect it against herbivorous animals generally. Furthermore, the aridity of the countries in which Castela exists, greatly reduces the competitive struggle.

The lower surface of the leaves, and to a lesser degree also the stems, contain a small fungus (rust-like) which appears to find lodging among the trichomes. Whether or not this parasite contains any toxic or otherwise therapeutically objectionable substances has not been ascertained.

The dried shrub is very annoying to handle because of the thorns and sharp-pointed terminal branches. It is very hard and woody and can best be broken in a larger mill very coarsely set. The Nixons emphatically urge the use of the "tendrils" (old, now obsolete term for younger branches) for medicinal use, which advice should be heeded for reasons indicated above.

Chemistry of Castela.—The usual reagents gave no indication of the presence of alkaloids. Fehling's solution gave a marked reaction for invert sugar. Charring some of the extract on platinum first developed the odor of burning caramel, ending with an odor of creosote. Shaking with chloroform gives rise to an emulsion which endures for many hours. Apparently this represents a colloidal phase with the mucilaginous substance so abundantly present in the leaf hypoderm that the ultramicroscopic examination of the aqueous infusion reveals abundant particles manifesting the characteristic Brownian motion, which colloidal particles evidently belong to the mucilaginous cell contents.

Calcium oxalate is abundantly present in the leaves and also in the stem parenchyma, occurring in the form of prismatic crystals and some aggregates. Chlorophyll is abundantly present in the leaf and in the younger branches. The total ash of the stems is 7.4 per cent. according to Bukey. Starch is sparingly present in the stems, more abundant in the root system. Granules small, simple to compound. A small amount of oil is present.

According to Bosman, Castela contains a glucoside to which he gave the name *castelin*, and to the hydrolization product of the glucoside he applied the name *castelagenin*. Castelin can be purified by repeated cyrstallization from water, from which it separates in long, white needles and has a melting point of 205° C. It dissolves in 85 parts of water at room temperature, and in 25 parts of water at

100° C. It is more soluble in ethyl alcohol and in cold concentrated hydrochloric acid, and gives a deep violet coloration with concentrated sulphuric acid. The anhydrous castelin is highly hygroscopic, taking up 8 per cent. of its weight of water on exposure to air for an hour. It has the formula $C_{15}H_{22}O_8 + 3H_2O$, and is dextrorotatory (+62.9°) in aqueous solution.

Castelin is readily hydrolyzed by dilute acids and alkalies, a 20 per cent. solution of hydrochloric acid being the most satisfactory hydrolizing agent. The yield of castelagenin is rather low, barely exceeding 20 per cent. Castelagenin is readily soluble in boiling glacial acetic acid, from which it crystallizes in a pure condition. It is insoluble in chloroform, ether or acetone, but is freely soluble in warm methyl or ethyl alcohol. It has a melting point of 240–241° C., and gives no coloration with concentrated sulphuric acid. It is soluble in cold phenol and dextrorotatory (+59°), and its reaction with sodium hydroxide and sodium carbonate indicate that it is lactonic in nature. On oxidation with 30 per cent. nitric acid at 150° C. it yields a minute quantity of crystalline acid (melting point 128–129° C.), which is somewhat soluble in ether and gives the fluorescin reaction and appears to be a dicarboxylic acid.

The bitter principle castelamarin can be deposited out from warm alcohol, appearing in the form of aggregates of slender needles (60 per cent. alcohol with a few drops of sodic hydrates solution, and precipitating with dilute hydrochloric acid). Bosman suggests that the bitter principle is closely related to the glucoside castelin, differing from it chemically by only two atoms of hydrogen. Castelamarin is exceedingly bitter and gives a deep blue coloration with concentrated sulphuric acid which fades to a dirty brown after a few minutes.

Since Putegnat (1883) claims to have isolated a bitter principle (amorphous) to which he applied the name "amargosin," according to the rule of priority in nomenclature, that name would be retained rather than "castelamarin."

In common with most higher plants, *Castela Nicholsoni* contains tannic acid. It also contains a small amount of oil and considerable mucilaginous matter, which occurs in the hypodermal tissue cells, especially abundant in the hypoderm of the leaves. The mucilaginous matter is colorless and tasteless and is readily soluble in water; forms an emulsion with chloroform but is thrown down by 50 per cent. alcohol. Among the other inert constituents present are a small amount of resin and considerable chlorophyll. As stated, the mucilaginous matter is especially abundant in the leaves and since this substance is undesirable in preparations intended for hypodermic administrations, and since the leaves are small and readily drop off, it is suggested that the leaves be discarded altogether, in making the purified dry extract.

The older branches are literally covered with crustose lichens and also foliose and fruticose forms, and since these saprophytes may contain toxic or otherwise therapeutically objectionable substances, it would appear highly desirable to remove the outer bark layers of the older branches by some suitable process, using only the inner parenchymatous and woody tissue; at least this would be desirable in preparing the drug for making the preparations intended for hypodermic use. The terminal branches of the younger plants or the recent growth (one to two years) are comparatively free from lichens.

In common with desert plants generally, *Castela Nicholsoni* is quite rich in

mineral salts, as chlorides, sulphates and carbonates, and the removal, wholly or in part, of these constituents, should be taken into consideration by pharmaceutical manufacturers.

Pharmacology and Toxicology.—Bosman speaks of castelin as the active principle (therapeutically) of *Castela Nicholsoni*, but so far no tests have been made to demonstrate that castelamarin is *not* the active principle despite the statement by Bosman that this substance is pharmacologically quite inactive (excepting the action on the coronary circulation). No observations are recorded as to the pharmacologic action of castelagenin nor is it known to what extent this product of the hydrolization of castelin occurs or develops naturally in the dry and aging drug. The indications are that all three substances occur in the growing plant, but that after drying and especially on exposure to light and moisture, and also during pharmaceutical manipulation, the castelin is gradually converted into castelagenin. Further investigations are necessary to clear up these points.

All of the pharmaceutical preparations, as well as the infusion, contain the three substances named (castelin, castelagenin, and castelamarin), as well as certain salts and also inert constituents. According to numerous laboratory tests the purified (detannated and degummed) solid extract which consists largely of the three constituents named is only $^1/_{20}$th or $^1/_{25}$th as toxic as is emetin hydrochloride. Death is due to gradual general paralysis, respiration ceasing before the action of the heart. The heart (in frogs) stops in diastole (auricular as well as ventricular). The comparative study of the toxicity of the solid extract of Castela and of emetin hydrochloride gave the following results.

Paramecial method (3 minutes)	1–25
Frog method (1-hour periods)	1–20
Gold fish method (1-hour periods)	1–22

It is rather remarkable that Castela and emetin should produce closely similar reactions in *Ameba caudatum*. Motion is slowed, trichocysts are ejected early and string out behind the organism as it moves along. Next there is a zig-zag forward motion, then a pin-wheel motion, finally all motion (excepting ciliary) ceases, the plasmic contents are completely expelled and only the external membrane, with the cilia still in active motion, remains.

Bosman made a series of tests, with the purified castelamarin, on isolated tissues and on tissues *in situ*, with apparently negative results. Strengths of solutions up to 1:500 were used but without any appreciable effects on the isolated intestine and the uterus of the non-pregnant cat. A negligible increase in tone was indicated. The most striking effect following the perfusion on the isolated mammalian heart with a 1–2000 solution was the constriction of the coronary vessels. This was indicated by a great retardation in the outflow, which was actually reduced to one-third and less. The conclusion reached by Bosman is that the bitter principle of Castela was a substance of low toxicity and of only slight pharmacologic activity.

Dr. P. I. Nixon of San Antonio, Texas, made some tests with the fluid extract of Castela on the amebæ of dysentery, declaring that this organism was very sensitive to the action of the drug, killing promptly in very high dilutions. The following is quoted from his article: "I give the results of a few experimental observations to show the amebicidal action of Chaparro amargosa. Under the microscope, 1:10,000 dilution of the detannated fluid extract at body temperature caused all *Entamoebae*

histolytica to cease moving instantly and to assume a spherical shape with sharp differentiation of ectoplasm and endoplasm; 1:100,000 dilution required from thirty to sixty seconds to accomplish the same results, and 1:1,000,000 from one to three minutes." These observations could not be verified by others, including the writer. In fact the usual saprophytic forms of amebae are even more resistant to the action of Castela than are the paramecia. In a dilution of 1:12 of the solid detannated and degummed extract of Castela the amebae were not killed for some time (ten minutes or longer) although there was noticeable an increase of the ectoplasmic zone while the endoplasm appeared to remain unchanged. A dilution of 1:9 killed *Paramecium caudatum* in three minutes; while the same organism was killed within the same period of time by a dilution of 1:225 of emetin hydrochloride, thus proving the latter substance to be 25 times as toxic as the former. However, it has been demonstrated repeatedly that the toxicity of a drug is not necessarily proportional to its therapeutic activity; nor does it follow that a therapeutic agent must yield test-tube or laboratory results in order to be of use therapeutically. Whether or not Castela kills the amebae of dysentery in a test-tube or on a slide is after all of minor importance. The clinical results have shown that in *Castela Nicholsoni* we have a drug of great promise in the treatment of amebic dysentery. It has apparently given results in cases that did not respond to emetin. It is far less toxic than is emetin. The prolonged use of ipecac in resistant cases of amebic dysentery has resulted in marked toxic manifestation, from which the patients fortunately recover completely as soon as that drug is discontinued. No such toxic effects follow the use of Castela. Dr. Boyers (Berkeley, California), in a verbal report, declared that the infusion of Castela gave rise to intestinal disturbances, without, however, giving particulars. Large doses (3 drachms of the fluid-extract) taken by the writer produced no marked disturbances of any kind. There was a slight laxative effect and the appetite was somewhat increased. The slight toxic effects reported by Dr. Boyers may have been due to the use of old lichen-covered stems. The rather negative results in amebic dysentery reported by Dr. Boyers may also have been due to the use of old more or less inert material.

Therapy of Castela Nicholsoni.—As has already been indicated, the principal use of the drug is in the treatment of amebic dysentery. Whether or not it is also of use in the bacillary forms of dysentery has not been definitely ascertained although Dr. Nixon declared that it is useless in such cases. The Nixons used the drug in the form of the infusion (of the color of weak tea) per mouth (teacupful doses) and also as enemas, continuing the treatment for some time after the stools have returned to normal. The beneficial results are apparent almost immediately. On the first sign of recurrence, the treatment is to be repeated. For details of the method of using Castela in amebic dysentery those interested should consult the articles by Knox, Nixon, and Sellards and McIver.

The therapeutic value of the drug in malaria has not been ascertained. It would be well worth while to give it a trial in this disease. It is suggested that for such a trial the dry extract be administered hypodermically in doses of not less than one gram (15 grains) daily, about the time the chill is to come on (sporulating stage of the malarial protozoan), and continued for a week at least.

Dr. Van Hoosen of Chicago tried the dry purified extract in a case of carcinoma of the uterus which did not respond to the action of emetin hydrochloride. The

drug (30 grains) was dissolved in 50 cc. normal saline and injected under the breast (connective tissue). Within an hour after the injection of the first dose there was some vomiting without intestinal disturbance, but no other untoward reactions. Vomiting did not recur on subsequent injections of like amounts, and it is believed that the vomiting following the initial dose was psychically reflex (anticipatory), as the patient had previously vomited after each dose of emetin hydrochloride. The outcome of the treatment in this case was not announced to the writer despite several inquiries verbally and *in lit.*

Pharmaceutical Preparations.—Sharp and Dohme of Baltimore, for a number of years, have been marketing the extract, the fluidextract, and gelatine coated pills of *Castela Nicholsoni.* The extracts are very dark in color and intensely bitter and somewhat astringent, but there is no acridity or pungency and even the most delicate tissues are not disturbed by it. The dose of the extract is 2 to 3 grains, of the fluidextract one drachm, and 1 to 3 pills. The fluidextract as well as the solid extract, despite the extreme bitterness, recall the taste of glycyrrhizin or licorice somewhat. The infusion (in hot water) as used by Dr. Nixon has the color of tea and is, of course, also intensely bitter. The author prepared a purified solid extract intended for hypodermic administration, as follows.

Extract for six hours one kilo of the coarsely broken recently gathered dry drug, in two kilos of hot distilled water, with occasional stirring. Filter through cotton and to the filtrate, when sufficiently cool, add 10 grams of powdered egg albumen, stirring until the albumen is mostly dissolved. Bring to a boil. The coagulating albumen takes up the tannic acid and the coarser impurities. Filter through one layer of coarse filter paper. Evaporate the filtrate to one-half volume, or less, at reduced pressure; and add an equal volume of 97 per cent. alcohol which throws down (coagulates) the mucilaginous matter, which is then removed by filtration, again using coarse filter paper, and then evaporate the detannated and degummed aqueous extract to dryness at reduced pressure, using porcelain-lined evaporating dishes. The dry extract is of dark brown color, very brittle and highly hygroscopic. The powder is of a rather light cinnamon brown color and must be kept in dry air-tight containers. On exposure to the air the powder soon becomes sticky due to the absorption of atmospheric moisture. It is readily soluble in water (either distilled or hydrant water, or in normal saline). For hypodermic use, dissolve the required amount of the powder in from 15 to 50 cc. of distilled water or in normal saline, and inject slowly. There are neither local nor systemic reactions. In a female cancer patient, a dose of 2 grams (30 grains), given interstitially (under the breast), vomiting (without purging) followed within an hour after the first dose, but subsequent injections (also 30 grains), were without any disturbing reactions of any kind (from verbal and *in lit.*, reports of Dr. van Hoosen of Chicago). The writer administered to himself 10-grain doses hypodermically on several occasions, without any appreciable reactions, either local or general. As far as known to the writer, no one else has administerd preparations of Castela hypodermically.

The Nixons originally used the freshly prepared tea of Castela in the treatment of dysentery. The infusion as well as the decoction deteriorate very readily on standing, due to bacterial invasion. The solid extract keeps fairly well, but it is nevertheless advisable to add a small amount of trikresol (0.25 per cent.) to the dry extract intended for hypodermic use.

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Plate I. Gross morphology of *Castela Nicholsoni*, Hooker. (*E. S. del.*, after Hooker.) A, portion of female plant; B, portion of a male plant; a, unexpanded flower; b, female flower, with 3 abortive stamens; c, single abortive stamen; d, stamens; e, single stamen; f, fruit (drupe); g, drupe cut open to show the seed with endocarp; h, drupe showing seed in position; i, transversely cut drupe; j, embryo; k, leaf, somewhat enlarged.

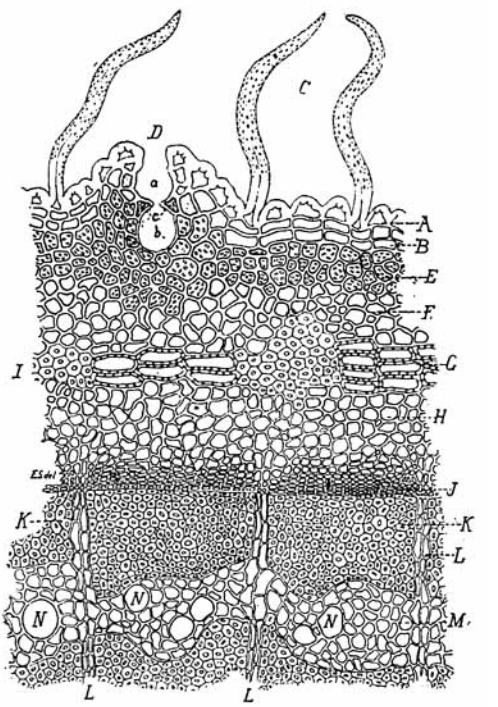

Plate II. Transverse section of the stem of *Castela Nicholsoni*, Hooker, ×450 (*E. S. del.*). A, epidermal layer; B, hypodermal layers; C, trichomes; D, water pores; a, antechamber, b, reservoir; c, guard cells; E, chlorophyll bearing parenchyma; F, outer bark parenchyma; G, sclerenchyma cells; H, inner bark parenchyma; I, groups of bast cells; J, cambium; K, wood parenchyma; L, medullary-rays; M, water-storing tissue; N, ducts, porous.

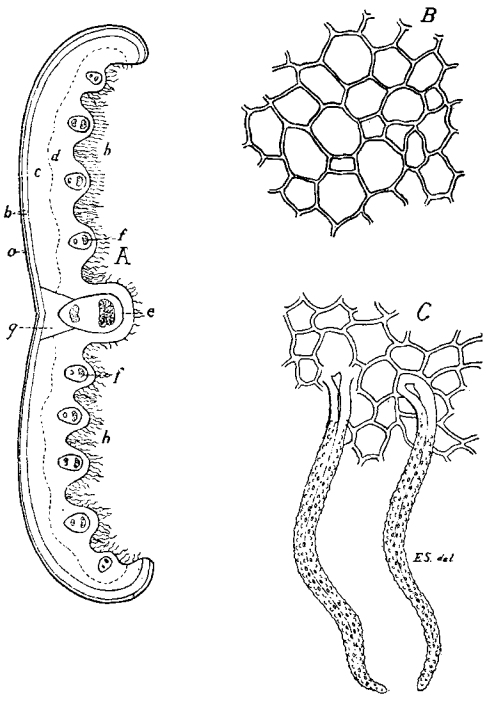

Plate III. Histology of leaf. B and C, ×450; A, ×60. (*E. S. del.*) Transverse section of leaf, diagramatic; a, epidermis; b, hypoderm; c, palisade tissue; d, spongy tissue, midrib; f, vascular bundles; g, mechanical tissue. B, upper epidermal cells, vertical view; C, lower epidermis, with trichomes, vertical view.

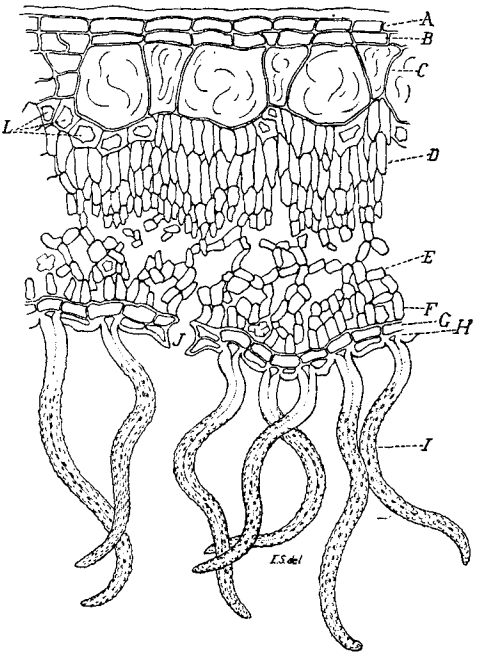

Plate IV. Transverse section through leaf, ×450. (*E. S. del.*) A, epidermis; B, first hypodermal layer; C, second, mucilage bearing hypodermal layer; D, palisade tissue; E, spongy tissue layer; F, single row of lower palisade tissue; G, lower hypodermal layer; H, lower epidermal layer with trichomes (I) and stomata (J); L, prismatic crystals of calcium oxalate.

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