Heterogeneous Polysaccharides

1. GENERALITIES: GUMS AND MUCILAGES

The terms gums or mucilages commonly designate polysaccharide macromolecules that dissolve more or less upon contact with water to form colloidal solutions or gels. The current trend is to abandon these terms in favor of the more general "vegetable hydrocolloids", or the even more global "vegetable polysaccharides". The term polysaccharide may appear to lack specificity (it applies to cellulose as well as to gum arabic), but it is sometimes difficult to delineate, biologically as well as chemically, concepts of gums and mucilages—and also pectins—therefore whenever possible we shall favor structural criteria to classify these polymers. We shall keep the term of gum for all exudates and we shall then distinguish neutral heterogeneous polysaccharides (mannans and derivatives), acidic heterogeneous polysaccharides (at first approximation these are the mucilages of classical texts), and galacturonans (pectins).

In addition to the medicinal interest of certain "mucilage-containing drugs" and of some gums, heterogeneous polysaccharides are of obvious industrial interest. However, we must point out that for purely economical reasons, they face fierce competition in polymers of bacterial or semisynthetic origin (such as cellulose derivatives). Only products such as guar (which may be rationally cultivated in modern agriculture) can defend their share of the market. This also appears to be the case for products authorized for the human diet that have specific properties (carob).

A certain number of criteria have been put forward to distinguish gums and mucilages. Gums are complex molecules, are always heterogeneous and branched, and contain uronic acids. They flow on the outside of the plant and are generally considered to result from a trauma (although tragacanth gum is stored *prior to* any aggression). They would arise from the transformation of parietal polysaccharides and maybe even from starch. Although it has been postulated that they are the manifestation of an adaptation to drought, their presence in plants of northern regions tends to weaken this hypothesis. Gums concrete by desiccation, they are insoluble in organic solvents, and this differentiates them from resins (which are most often terpenoid).

Mucilages on the other hand are considered to be normal cell constituents, preexisting in specialized histological formations (cells or canals) that are common in the external tegument of seeds. Fairly widely distributed, they are common in Malvales (acidic mucilages) and Fabales (neutral mucilages of the endosperm). Water-retaining agents, they would have an active role in germination; their formation would involve the Golgi apparatus.

2. GUMS (EXUDATES)

1. Group **A**. This group, which includes *Acacia* gums, is based on a galactan-type backbone substituted by L-arabinose units, and by branched oligosaccharides containing another monosaccharide (L-rhamnose, D-xylose) and D-glucuronic acid. The polysaccharide is often associated with a protein.

2. Group **B**. It includes gums similar to pectins: (1—>4)-linked D-galacturonic acid chains substituted by short chains containing L-arabinose, D-glucuronic acids, and D-galacturonic acids. L-Rhamnose occurs in the main chain, sometimes as frequently as every other sugar: such is the case of karaya gum. In a few rare cases, both types of molecules (type A and type B) coexist.

3. Group **C**. Gums in this group are uncommon 1—>4-β-linked xylans and are highly substituted by miscellaneous monosaccharides (L-arabinose, L-galactose, D-glucuronic acid, and so forth).

4. Group **D**. The central chain results from alternating (1—>4 – 1—>2) D-glucuronic acid and D-mannose. The hydroxyl groups at C-3 of most mannoses are substituted by sequences analogous to those of group A. Gum ghatti is an example of this type of structure.

Although gums occur in all of the vegetable kingdom, they are found mostly in a few families, including the Mimosaceae, Rosaceae, Combretaceae, Burseraceae, and Rutaceae. The composition of a gum is characteristic of one species, but can fluctuate slightly as a function of geographical origin and environmental factors. Their molecular weight varies from 2×10^4 to 10^6 (polydispersity is often important). Most gums are partially methylated (e.g., on the hydroxyl group in C-4 of glucuronic acid, on the hydroxyl group in C-3 of rhamnose) or acetylated. Carboxylic functions may occur as salts.

Most gums dissolve in water to form viscous solutions; some are completely insoluble and form gels. Dilute solutions of these gums (1% or less) generally precipitate upon addition of ethanol. They are optically active, and this is an important element in their identification. Acidic hydrolysis followed by TLC of the free monosaccharides is also a good means of identification of a gum: it is systematically used by pharmacopoeias (it allows detection of mixtures or additives at the same time).

• KARAYA GUM or STERCULIA GUM
Sterculia spp., Sterculiaceae

Karaya gum is "the air-hardened product of the natural or incision-induced viscous exudate from the trunk and branches of *Sterculia urens* Roxb., of *Sterculia tomentosa* Guill. & Perr. and of other close species" (Eu. Ph. 10th Ed.).

Botanical Origin. *Sterculia* are trees with large leaves with five lobes, with apetalous flowers, and with fruits composed of lignified follicles. The cortical parenchyma of the trunk and of the branches contain secreting canals within which the gum accumulates. In addition to the species listed above, the literature mentions *S. tragacantha* Lindley, which is a western African species, as is *S. tomentosa*. These African species produce what the French call "gomme M'Bep"; in contrast, "karaya *" gum is produced by *S. urens* which grows in the mountains and dry plateaus of central and northern India. The gum, preferably collected before and after the monsoon season, is obtained after tapping or else blazing or charring. The exudate is collected, freed of residual bark, and sorted by foreign matter content and color. The commercial product is generally pounded or ground (but the powder is harder to conserve).

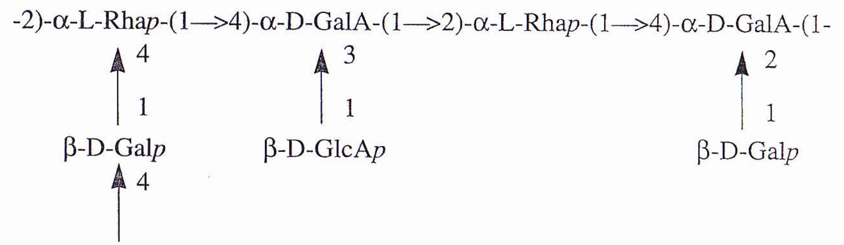
The Drug. The drug consists of irregular, translucent, and pinkish-white to brownish masses which smell of acetic acid. This gum is sparingly soluble in water: the gum particles absorb water and swell to considerable proportions, forming a highly viscous suspension. The hydration process is slow: the preliminary mixing of the gum with an alcohol facilitates the preparation of a homogeneous dispersion. The viscosity of the dispersion depends on the particle size of the gum. If the concentration increases (2-3%), a paste forms that behaves as a gel and becomes highly adhesive at higher concentrations (20-50%).

Composition. The gum is of type B (glycanorhamnogalacturonan): central backbone with a basic unit consisting of alternating α-D-galacturonic acid linked through the C-4 position and α-L-rhamnose linked through the C-2 position. The chain is substituted on the galacturonic acid hydroxyl groups in C-2 or C-3 and on some of the rhamnose hydroxyl groups in C-4 by D-galactose and D-glucuronic acid. The uronic acid content is about 40% and the degree of acetylation is about 8%.

Tests. Several reactions allow verification of its identity: acidity (release of acetic acid upon heating), staining pinks with ruthenium red, characterization of uronic acids after sulfuric hydrolysis (using dihydroxynaphthalene).

The tests include the following:

1. determination of the pH of a 1% aqueous solution free of carbon dioxide: it must be not more than 5.5;
2. characterization by TLC of galactose and rhamnose in a sulfuric hydrolysate of the gum (revealed by aminohippuric acid);
3. determination of the swelling index which must not be less than 13 (in a 37% [v/v] ethanol solution);
4. quantitative estimate of foreign matter (elements insoluble in acidified [HCl] water brought to a boil): <5%.



Repeating unit characteristic of Sterculia *gum*

Uses. Initially considered to be a substitute for tragacanth gum, karaya gum has many advantages that explain its extensive use in pharmacy. Its ability to form viscous dispersions while swelling considerably make it a bulk laxative; it will not ferment, and is not absorbed, degraded, or toxic. It is indicated in the symptomatic treatment of constipation [French Expl. Note, 1998] and prescribed alone or in combination with various active principles (aloe, buckthorn, meprobamate, polyvinylpolypyrrolidone, aluminum silicate, magnesium sulfate and oxide). The gum and its combinations are contraindicated in case of pyloric stenosis, and must be used with caution in case of megacolon due to alteration of colon motility. Karaya gum is also used for its zero-calorie bulk to provide a feeling of satiation and as such, it is traditionally used as an adjunct in weight loss diets. Its adhesive properties make it useful for colostomy apparati and to affix dental prostheses. It is seldom used in the food industry, however it is an interesting aid in pharmaceutical technology, as well as in the cosmetics industry.

• Gum arabic, *Acacia* spp., Mimosaceae

According to the 3rd edition of the European Pharmacopoeia, gum arabic is the air-hardened, gummy exudate which flows, naturally or upon tapping, from the trunk and branches of *Acacia senegal* (L.) Willd., and other *Acacia* species of African origin. The Pharmacopoeia also describes the nebulisate obtained from a solution of the gum.

The Plant. This acacia, known as *verek* in western Africa (but also as *hashab* in Sudan), is a small tree (4-6 m) with curved thorns, with compound bipinnate leaves, and with regular flowers grouped in elongated cylindrical spikes. The flowers have a small white corolla, and long and numerous stamens. The fruit is a straight pod constricted between the seeds. This acacia and closely related species that produce gum arabic grow wild in the African near-desert, from the Atlantic Ocean to the Red Sea.

ACACIA SENEGAL willd.

Mauritania. Although the rational exploitation of plantations is feasible, an important part of the market seems to be supplied by the harvest of gums exuded by wild trees.

The work on acacias takes place during the dry season, as the leaves fall. Both the gum that exudes naturally, and that formed after tapping, which consists of making a transverse incision, then pulling off the bark on both sides of the cut, are collected. The strips of bark are removed without injuring the cambium; the latter regenerates the phloem and the gum exudes for a few weeks. The gum (one to two kg per tree and per year) is collected and sorted into different commercial categories, essentially by color criteria. Over the last decade, climatic variance and political unrest — but also, it seems, damage caused by grasshoppers — have caused large market fluctuations, including, during certain years, a substantial decrease in supply, which in turn led the usual consumers to resort to substitutes, for example other gums. Some also recommend lipophilic starches (e.g., Purity-Gum 1773 ®, N-Lok ®) to stabilize emulsions (non-alcoholic beverages) as well as to encapsulate fragrances.

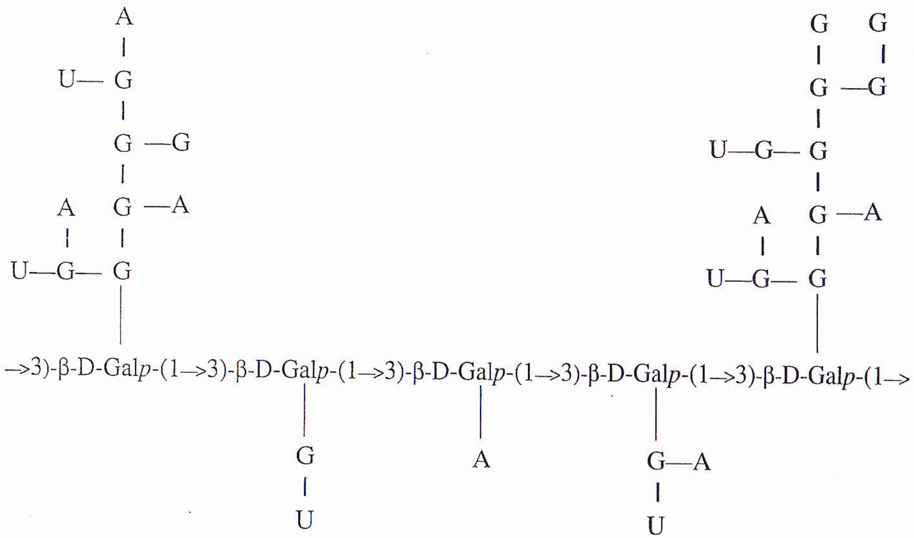
The Drug. The gum consists of spheroidal masses 1-3 cm in diameter that are brittle, yellowish-white or pale amber, opaque, often broken into irregular fragments, angular, glassy, and transparent. The gum is odorless, tasteless, and adheres to the tongue. As a powder, it is more or less yellowish-white and dissolves very slowly in twice its mass of water to form a solution that is viscous, adhesive, weakly acidic, and rotates polarized light (levorotatory).

Chemical Composition. The raw gum contains 10-15% water, some tannins (especially in the colored drugs), oxidases, but no starch.

The chief constituent is an acidic polysaccharide which occurs in the native state as a salt (of calcium, and to a lesser extent, of magnesium and potassium). The polymer varies with the tree, its geographical origin, and the harvest time; its molecular weight ranges from 3×10^5 to 10^6, its $[\alpha]_D$ is –30°±4 (FAO). Its analysis reveals the presence of several monosaccharides: D-galactose (32-50%), L-arabinose (17-34%), D-glucuronic acid (13-19%), and L-rhamnose (11-16%).

The basic structure is that of a 1—>3 galactan substituted by arabinose units (isolated or in short chains) and by complex oligosaccharides comprising D-galactose, L-arabinose, L-rhamnose, and D-glucuronic acid.

Properties and Uses. Egyptian hieroglyphs document the ancient use of this drug which has been traded for at least four thousand years. Gum arabic is an emollient and bechic, and is used in the composition of classical preparations such as French official pastes. Unlike galactoglucomannans and mucilage from plantains, its daily absorption has no effect on cholesterolemia. It is readily soluble in water (solutions of concentration greater than 50% can be prepared) and forms viscous solutions the behavior of which is first Newtonian, then pseudoplastic at higher concentrations. The viscosity of the solutions depends on the origin of the drug (including species



Gum arabic : structural hypothesis

G = β-D-Gal*p*
A = short chains of L-Ara*f* linked (1→3)
or α-D-Gal*p*-(1→3)-L-Ara*f*
U = α-L-Rha*p*-(1→4)-β-D-GlcA or β-D-GlcpA (4-OMe)

Redrawn from Stephen, A.M., Churms, S.C. and Vogt, D.C. (1990). Exudate Gums, *in* "Methods in Plant Biochemistry, 2: Carbohydrates", (Dey, P.M., Ed.), p. 483-522, Academic Press, London.

it. It is compatible with most other plant hydrocolloids and with the majority of alkaloids, but incompatible with gelatin, iron salts, and phenols (e.g., thymol, eugenol, morphine).

The viscosity of its solutions and their fairly good stability in acidic conditions make it an interesting pharmaceutical aid: a stabilizer for suspensions, but also an emulsifier, an agent for encapsulation of fragrances by nebulization, and an additive for the preparation of solid formulations designed for oral administration.

In food technology it is a totally non-toxic stabilizer and emulsifier (Eur. id. code E414) which is also neutral, odorless, tasteless, colorless, and stable. It can also be used for its ability to form coacervates with proteins.

Tests. The determination of the optical activity of a solution of the gum, and TLC analysis (revealed by the aminohippuric acid reagent) of the monosaccharides

drug (presence of L-arabinose, D-galactose, L-rhamnose, and absence of D-glucose). The identity is confirmed by precipitation reactions (alcohol, lead acetate).

The tests include the verification, on a 10% solution, of the absence of starch and dextrin (absence of blue or reddish color with iodine), of sucrose and fructose (no color with chlorohydric resorcinol), tannins (none of the characteristic reaction with ferric chloride), agar, karaya gum (no color with ruthenium red), and tragacanth gum * (none of the characteristic color with iodine). In addition, the drug must pass the common general tests (loss on drying, sulfated ashes, insoluble matter). The gum must pass a limit test for total viable aerobic count (10^4 micro-organisms per gram) and a test for *Escherichia coli*.

• TRAGACANTH GUM , *Astragalus gummifer* Labill., Fabaceae

The 3rd edition of the European Pharmacopoeia specifies that this gummy air-hardened exudation that flows naturally or by incision from the trunk and branches of *A. gummifer* may also arise from certain other species from western Asia.

The Plant, the Drug. *A. gummifer* is a bushy and very thorny subshrub (0.5-1 m). The leaves are pinnately compound and have small grayish folioles that drop precociously to leave a thorny rachis. The pale yellow flowers are gathered into racemes. The fruit is a small fuzzy 1-seeded pod.

Astragalus are from the mountain deserts of western Asia: from the south of Iran to Kurdistan and Armenia, from Syria and Iraq to Khorasan and Afghanistan.

In the present case, the gummosis is centripetal and the gum accumulates in the medulla and the medullary rays, the cell walls of which later disappear: an incision of the branch provokes immediate exudation of the gum which is thrust outward as a viscous ribbon, worm-shaped (accidental trauma), or fan-shaped (incision). Traditionally, the basis of the main stem is exposed out of the earth and deeply incised: after at least 48 hours the exudates are collected, gathered, and sorted. The least colored batches are considered of highest quality.

Tragacanth gum is odorless and tasteless, consists of thin ribbons (30 x 10 x 1 mm) that are flattened, white, translucent, horny, finely striated longitudinally and ondulate in the transverse direction. The microscopic examination of the powdered drug reveals the presence of rounded starch granules (4-10 μm) with a central hilum. The stratified cellular membranes that surround the starch grains are stained purple by a zinc chloride and iodine solution.

* At times falsification occurs using gums of inferior quality or performance that are difficult to detect. Such is the case of "gum combretum", secreted by *Combretum nigricans* Lepr. ex Guill. & Perr.: the structural difference may be shown by spectrometric methods. Anderson, D.M.W., Millar, J.R.A. and Weiping, W. (1991), The Gum Exudate from *Combretum nigricans* gum, the Major Source of West African "Gum Combretum"

Chemical Composition. In contrast to gum arabic, tragacanth gum does not contain oxidases, but comprises about 3% starch and 3-4% minerals. The raw gum is considered to be a mixture of two polysaccharides: tragacanthin (30-40%), which is neutral and soluble in water and alcohol mixtures, and dissolves in water to form a colloidal solution, and bassorin (60-70%), which is acidic, precipitates in the presence of ethanol, and swells in the presence of water to form a gel. Tragacanthin is an arabinogalactan (1—>6, 1—>3), is almost neutral, and has a galactose backbone. Bassorin (or tragacanthic acid) on the other hand is a partially methylated glycanogalacturonan of molecular weight approaching 850,000, built from four monosaccharides: D-galacturonic acid, D-galactose, D-xylose, and L-fucose. The central backbone of the molecule is a chain of 1—>4-linked galacturonic acids; the chain is substituted by xylose units or by disaccharides (fucoxylose or galactoxylose).

Tests. Gum identification is accomplished, among other means, by microscopic examination (see above) and by TLC analysis of a sulfuric hydrolysate. Spraying with aminohippuric acid reveals the constituent monosaccharides (fucose, xylose, galactose, arabinose) and allows verification of the absence of methylcellulose.

The test *per se* includes the determination of the flowing rate in a graduated tube, as well as a series of reactions to detect other gums (gum arabic, karaya gum) and foreign substances, which must not exceed 1% by weight. The gum must pass a limit test for total viable aerobic count (not more than 10^4 micro-organisms per gram) and tests for *Escherichia coli* and *Salmonella*.

Uses. A very ancient drug (it was known and prized by Greek physicians), tragacanth is indicated for the symptomatic treatment of constipation [French Expl. Note, 1998]. It is mostly used as a pharmaceutical aid. Dilute solutions (0.5-1%) are very viscous, stable in acid and heat, compatible with most plant hydrocolloids, and easy to conserve; they have a pseudoplastic behavior which, together with their anionic character, make them good stabilizers for suspensions. The product can also be used to form and stabilize emulsions: a bifunctional emulsifier, it increases the viscosity of the aqueous phase *and* decreases surface tension at the interface in O/W emulsions. Because replacement products exist (particularly xanthan gum and certain alginates), and because of the relative scarcity of the product (a labor issue), this gum, as gum arabic, is relatively seldom used in food technology, in spite of being an authorized thickener (Eur. id. code E413).

• Gum Ghatti,
Anogeissus latifolia (DC.) Wallich., Combretaceae

This gum is the viscous exudate of a tree of the forests of India and Sri Lanka. Produced and collected as is karaya gum, it is a complex polysaccharide which contains D-mannose, D-galactose, L-arabinose, D-xylose, and D-glucuronic acid. When

stabilizer, it is being replaced by other polysaccharides (guar and cellulose derivatives).

3. POLYSACCHARIDES DERIVED FROM MANNOSE - "NEUTRAL MUCILAGES"

Mannose is a monosaccharide that occurs frequently in polymers. Mannan itself is rare. This compound is a polymer consisting of a linear chain of (1—>4)-β-linked D-mannose units and is strictly insoluble in water: it is the chief constituent of vegetable ivory. Also called corozo, this *ivory* is in fact the albumen of the seed of a Palmae (*Phytelepas macrocarpa* Ruíz & Pavón) called ivory nut or tagua nut, and it was used during the nineteenth century to manufacture buttons and miscellaneous objects.

Heterogeneous polysaccharides comprising mannose are more frequent:

1. **Glucomannans**

In these polymers 20 to 50% of the D-mannose units of the chain are replaced by D-glucose. The glycosidic linkages are again (1—>4)-β; there may be several consecutive D-mannoses, but the glucose units remain isolated. Their DP ranges from 100 to 5,000 and they dissolve in water to form very viscous solutions. They are constituents of parietal hemicelluloses, more abundant in Gymnosperms than in Angiosperms, common in the subterranean organs of various Monocotyledons, and they accumulate in the tubers of *Amorphophallus konjac* Koch.

2. **Galactomannans**

In these molecules the hydroxymethyl group at C-5 of certain D-mannose residues of a mannose polymer chain is substituted by a D-ga-lactose linked α. The percentage of substitution varies from 30 to nearly 100% with the plant species. With a DP ranging from 1,000 to 10,000, they are water soluble, except for the least substituted representatives. They are present in various seeds (e.g., Annonaceae, Convolvulaceae, Palmae), constitute an extracellular deposit in the endosperm of the seeds of Fabales, and can represent up to 40% of the weight (e.g., carob seed).

3. **Galactoglucomannans**

The central chain is of the same type as that of glucomannans, and a variable number of mannose units within it are substituted on C-6 with an α-linked *O*-D-galactose moiety. A common component of hemicelluloses, they sometimes accumulate in seeds (for example in Judas tree, *Cercis siliquastrum* L., Cæsalpiniaceae).

• Carob tree,
Ceratonia siliqua L., Cæsalpiniaceae

The albumen of the seeds of this tree constitutes locust bean "gum". This product, which is not a gum, is commonly called locust bean flour in France. This latter term correctly reflects the origin, but can lead to confusion in that the dehydrated carob pulp is also on the market under the same term of flour or carob. Most of the world production (245,000 t) is directed toward industrial uses. Half the market is supplied by Spain. Other major producers are Italy, Morocco, Portugal, Greece, and Turkey (FAO data, 1998).

The Plant, the Drug. A large evergreen tree of the Mediterranean rim, the carob tree has compound pinnate leaves with 5-11 tough and shiny folioles, and small reddish flowers without corolla, grouped in axillary racemes. The fruit is a dangling, thick, and tough pod containing 12 to 16 flattened seeds separated by pulpous septa. The constant weight of the seed explains its ancient use as a unit of weight (1 carat = 200 mg).

The seeds are softened by steeping, freed of their envelopes and germ, and then the albumen is ground. The particle size determines the commercial quality of the powder. Some manufacturers also commercialize a purified flour obtained by dissolving the seed powder in hot water, precipitating the solution by adding ethanol, and recovering and drying the precipitate.

Chemical Composition. Carob "gum" is composed of an almost pure D-galacto-D-mannan (90-95%). This polymer is formed by a sequence of 1—>4-linked β-D-mannose with lateral branches of only one α-(1—>6)-linked α-D-galactose unit. On average there is one D-galactose unit per four D-mannose units. Branched segments would alternate with non-branched ones. *C*-glycosylflavones have been identified in the cotyledons.

The fruit pulp is poor in lipids (0.4-0.8% of the dry weight) and proteins (2.7-3%), contains 40-50% soluble sugars, cyclitols (especially pinitol), and condensed tannins (20%). After pulverization and roasting, it develops a cocoa odor (it is a potential cocoa substitute).

Properties of the Gum. Partially soluble in cold water, locust bean gum dissolves well in hot water (80°C) and gives, upon cooling, pseudoplastic solutions of high viscosity that withstand large changes in pH (3-11) and the addition of mineral salts. It acts in synergy with carrageenans to form elastic gels (the synergy is explained by associations formed between the non-substituted poly-M zones and the carrageenan double helices). It also interacts with guar gum and xanthan gum to form firm gels. Solutions of locust bean gum form gels in the presence of sodium borate in alkaline medium.

Uses

• **In therapeutics**. Carob flour (dried and ground mesocarp pulp) associated with the aleurone of sunflower and rice (or with treated starch) constitutes an absorbent preparation proposed in the symptomatic treatment of diarrheas in the infant and the small child. In the first 24 hours when carob or its combinations are administered, the only other substance taken should be water, to fulfill the need for hydration; later, feeding is restarted progressively. Carob may be diluted in water or milk, but must not be boiled.

The mucilage extracted from the endosperm is a thickening preparation that can be given to infants subject to vomiting. The French Explanatory Note of 1998 specifies that the fruit devoid of seeds is traditionally used for the adjunctive treatment of the painful component of functional dyspepsia and in the symptomatic treatment of mild diarrhea.

• **In dietetics**. Devoid of nutritional value, locust bean "gum" thickens rations without modifying the caloric intake. Thus it can be used "traditionally" as an adjunct in weight loss diets [French Expl. Note, 1998].

• **In the industry**. Due to their adhesive and thickening properties, locust bean "gum" solutions find many uses in food technology, mainly in the formulation of fresh or frozen milk products (creams, ice creams: Eur. id. code E410), but also—at least in North America—in bakery products (like guar, it helps the dough rise). The pharmaceutical and cosmetics industry, and numerous other industries (textile, paper) use it widely; they can also use semisynthetic derivatives prepared from the "gum" (e.g., hydroxyalkyl ethers, calcium salts of carboxygalactomannans).

• Guar plant,
Cyamopsis tetragonolobus (L.) Taubert, Fabaceae

Although it is common to speak of *guar gum*, this is an incorrect use of the word gum, since this product—also called *guaran*—does not result from an exudation subsequent to some trauma, but from grinding the seed albumen (Eur. Ph., 3rd Ed.). The pharmaceutical industry and food technology also use "guar galactomannan" widely; this product results from the grinding of the [seed] albumen followed by partial hydrolysis (Eur. Ph., 3rd Ed.).

The Gum: Origin and Structure. *C. tetragonolobus* is an annual herb cultivated in India and Pakistan, as well as in the United States (Texas) and in Central America. After elimination of the germ and of the envelopes, the endosperm is ground to yield the commercial product.

As in the previous case the polymer is a D-galacto-D-mannan formed by a sequence of 1—>4-linked β-D-mannose units with lateral branches of only one α-(1—>6)-linked α-D-galactose unit, but here the D-galactose:D-mannose ratio is close to one for two

Identity and Tests. Guar galactomannan is a white to creamy white powder, is practically insoluble in organic solvents, and gives an aqueous solution of variable viscosity. It is identified by its ability to form a gel in the presence of sodium borate and by the TLC characterization of mannose and galactose in the residue of hydrolysis by a trifluoroacetic acid solution. The tests include mainly verifying the absence of other gums (tragacanth, sterculia gum) and of algae polysaccharides (examined under a microscope, none of the structures are stained by ruthenium red); a nitrogen determination (i.e., a protein quantitation, <5%); a quantitation of insoluble matter after heating in dilute sulfuric acid (<7%); a measurement of apparent viscosity (rotating viscometer); microbial contamination: limit test for total viable aerobic count (not more than 10^3 micro-organisms per gram), tests for *Escherichia coli* and *Salmonella*.

The assay for guar is practically identical. Since the product does not get hydrolyzed, it is possible to identify it by microscopic examination of the albumen cells.

Properties. Guar gum, in fact as pectins, has the attention of nutritionists because of the interferences that it seems to cause, as do other "soluble fibers", with the metabolism of sugars and lipids. In regard to sugar metabolism, several experiments conducted in normal and diabetic subjects tend to demonstrate that the addition of guar to the food ration decreases hyperglycemia and post-prandial insulinemia. This effect alone is insufficient to normalize glycemia in diabetic subjects (yet some consider it favorable), and would be linked mainly to the high viscosity of guar which delays gastric emptying and reduces the rate of absorption of sugars in the intestine. In regard to lipid metabolism, the daily intake of guar gum decreases serum levels of cholesterol and LDL without notably affecting other lipoproteins, and without decreasing blood triglycerides (see in the previous chapter: dietary fibers).

Uses. Although guar gum may be included in the composition of diets for diabetics, it is of interest mostly in diets designed to decrease serum levels of cholesterol, a risk factor in cardiovascular disease. Combined with a diet low in lipids and high in carbohydrates, it can help remedy a moderately elevated serum cholesterol level temporarily. In practice, (concentrated) preparations based on guar do not taste very good and can induce minor digestive disturbances (flatulence, nausea): pectins are often preferred (15 g/day) and they have the same properties. Guar powder, once flavored, is recommended as "appetite suppressant".

Guar gum is also used, in combination with an intestinal protective agent (montmorillonite) in the symptomatic treatment of colopathies with constipation. Contraindications and precautions are the same as for karaya gum (risk—fortunately minimal—of formation of a bezoar in the esophagus or the small intestine).

Guar solutions (1% and less) are stable at pHs ranging from 4 to 10.5 and are compatible with most other plant hydrocolloids. The viscosity of their solutions is substantially increased when xanthan gum is added. It is an emulsifier and, under certain conditions, a gelifier. Pharmaceutical technology uses it occasionally and the agricultural and food industry are huge consumers because of its thickening properties (Eur. id. code E412). Other industries are also guar users: paper, mining (flocculation, flotation, filtration), water treatment, textiles, and more.

As in the case of cellulose, derivatives may be prepared (hydroxypropyl, carboxymethyl) that are essentially designed for industrial applications (textile, refinery, mining).

● KONJAC (konyaku), *Amorphophallus konjac* K. Koch, Araceae

A. konjac, like the numerous other species of the genus *Amorphophallus*, is originally from Asia; it is cultivated, especially in Japan. A voluminous tuber, a large leaf with three deep lobes, and a solitary foul-smelling flower with a purplish-black infundibuliform spathe and a long spadix characterize this Araceae.

In the tuber, a 1—>4-β-linked glucomannan accumulates (its D-glucose: D-mannose ratio is 1:1.6); the main chain is partially substituted mostly on the hydroxyl groups at C-3 by D-mannose or D-glucose. The DP of the polymer seems to vary with the geographical origin. The presence of a glycoside of 3,4-dihydroxybenzaldehyde has been reported in the commercial flour.

Traditionally the tubers are cut, dried, and milled. The resulting flour can be incorporated in foodstuffs (bread). In the last few years, simple forms, based on konjac flour or konjac glucomannans, have become available on the market (capsules, jelly). These preparations are recommended as adjuncts in low-calorie diets and to control the blood cholesterol level. Some studies in animals and in humans indicate a potential for these glucomannans, particularly to significantly reduce cholesterolemia and LDL-cholesterol. This activity is no surprise given the structural similarity between konjac glucomannans and products such as guar. More specifically, and unlike other soluble fibers, konjac glucomannan may have a clear activity on HDL-cholesterol and triglyceridemia. Complementary studies remain to be conducted; it is also important to define quality criteria for this drug which does not seem to appear in any pharmacopoeia.

● FENUGREEK, *Trigonella foenum graecum* L., Fabaceae

The Plant. Fenugreek is an annual herb with trifoliolate leaves on a long petiole. The flowers, solitary or in pairs, have a creamy white corolla with a posterior triangular petal. The fruit is an elongated arched pod, containing 10 to 20 very hard seeds (Eur. Ph., 3rd Ed., 1999 add.), flattened, with a brown to reddish-brown tegument marked with a groove that defines two uneven parts. Of oriental origin, the plant is cultivated on the Mediterranean rim.

Chemical Composition. The odor of the seed is linked to numerous volatile

PLANTAGO MAJOR L.

3-hydroxy-4,5-dimethyl-2[5H]-furanone. Rich in proteins (30%), the seed contains lipids (7%), *C*-flavonoids, and many sterols. Carbohydrates are particularly abundant: fibers (cellulose, hemicellulose) and soluble galactomannan (galactose: mannose ratio = 1.5:1). The seed is also a potential source of sapogenins that may be used for the semisynthesis of steroids (3,26-diglycosides of furost-5-enetriols and related derivatives yielding, among others and by degradation, diosgenin and yamogenin).

Properties and Uses. The seeds are recognized as being devoid of toxicity and known for their antidiabetic, blood cholesterol-lowering, and blood lipid-lowering properties: experimentally they decrease post-prandial glycemia in the diabetic rat and dog. Analogous effects have been reported in normal or diabetic humans. The fractionation of seed constituents, and the biological evaluation of the fractions, show that the antidiabetic and blood cholesterol-lowering activities are linked to the fiber-and galactomannan-rich fraction. The fraction that contains saponins is only active on elevated blood cholesterol levels. (Even if the structures involved are different, this could be another occurrence of an activity observed with other saponin-rich species capable of insolubilizing intestinal cholesterol [soapbark tree, p. 710, alfalfa, p. 715].)

Currently, the only indication approved in France for phytopharmaceuticals based on fenugreek seeds is the following: "traditionally used to facilitate weight gain" [French Expl. Note, 1998, orally]. In Germany, Fenugreek seed is official (DAB 10) and approved for the same indication; it is also used externally, as a cataplasm for local inflammations.

• Faba bean, *Gleditsia triancanthos* L., Broad bean, *G. ferox* Desf., Cæsalpiniaceae

The long arched pods of these trees, sometimes cultivated in Europe for ornamental purposes, provide seeds rich in galactomannans. The uses of the albumen powder are currently very limited. Officially, the seed may be commercialized in France in the category of "bulk laxative", following an abridged application dossier for a marketing authorization [French Expl. Note, 1998]. (For information on the use of laxative herbal remedies, see p. 424.)

• Peruvian gum, *Cæsalpinia spinosa* (Molina), Kuntze, Cæsalpiniaceae

Peruvian gum (= *huarango* or Peruvian carob) is obtained by grinding the endosperm of the seeds of this tree from northern South America and from Africa. It is a soluble galactomannan and its galactose:mannose ratio is intermediate between those of carob flour and guar. The strength and elasticity of its gels can be increased by the addition of xanthan gum (E417). The pod powder can be used for

4. ACIDIC HETEROGENEOUS POLYSACCHARIDES - "ACIDIC MUCILAGES"

Attempting a chemical classification of structures that are mostly ill-known can be quite a challenge, thus we shall group here, on the basis of their botanical origin and structural analogies, drugs that the majority of authors agree to consider as mucilage-containing drugs, no matter how blurry the concept.

A. Mucilage-containing Plantaginaceae

Several species in the genus *Plantago* provide drugs used in pharmacy: plantago seed, psyllium seed, plantain seeds, or ispaghula owe their laxative properties to very hydrophilic polysaccharides, and the leaves of certain plantains indigenous to France, based on tradition, are used in phytotherapy. Other species of the genus are used elsewhere in the world, for example *P. asiatica* L., the seed (*cheqianzi*) and leaf (*cheqiancao*) of which are, according to the traditional Chinese pharmacopoeia, expectorant, diuretic, and antimicrobial.

Psyllium husk and Psyllium

Properties. Ispaghula (seed and seed tegument) and psyllium (seed) are categorized as "bulk laxatives" [French Expl. Note, 1998]. Their effect, confirmed by several clinical studies, is purely mechanical and linked to their mucilage: the polysaccharide macromolecules, which ferment only to a small extent, absorb a large volume of water and form, in the colon, a voluminous gel that increases the bulk, water content, and acidity of the stool, stimulates peristalsis, and facilitates bowel movements with virtually no alteration of the transit period (in the absence of constipation). The mucilage is not depolymerized in the small intestine and is barely degraded by colon bacteria.

Several publications report metabolic activities for these mucilages, especially that of ispaghula, namely a decrease of post-prandial hyperglycemia—it is postulated that the increase in viscosity in the small intestine slows down the resorption of sugar *—and a cholesterol-lowering activity similar to that of galactomannans or pectins. The mucilage is thought to increase the fecal elimination of bile acids and cholesterol, and to decrease their intestinal reabsorption by binding to them. It has also been postulated that C2 and C3 aliphatic acids produced by the bacterial flora of the colon partially inhibit the hepatic synthesis of cholesterol. Since the late 1980s, several double-blind clinical trials have shown that the daily consumption of psyllium ** p. 106 (10 g/day, preferably mixed with food) leads to a modest decrease in total cholesterol (4-8%) and LDL-cholesterol (8-13%), but has no effect on triglyceridemia or HDL-cholesterol. Therefore, psyllium is not efficacious for lowering hypercholesterolemia. In combination with a proper diet *, it can help control a moderately elevated cholesterolemia, but the corresponding long-term clinical benefit remains to be confirmed. Other studies report its use in cases of irritable colon, but it appears that for this symptomatology, the effect of the drug is hardly different from that of a placebo; this is no real surprise in light of the known psychological component of this syndrome. Ispaghula and psyllium seed do not have major side effects (eventually they may cause a sensation of bloating); their toxicity is negligible: only a few exceptional cases of allergic reactions induced by the ingestion of seeds or by psyllium dust have been documented.

Uses. Different forms of psyllium are currently commercialized: drug *au naturel* or mucilage extracted from the seeds. The seeds are taken by the tablespoon (1-2) and their administration must be followed by that of an adequate volume of water (150 mL for 5 g, according to the German Commission E monograph). The mucilage itself (ispaghula mucilage, "psyllium seed hemicellulose") be it a powder or granules—not to be chewed—is also to be taken with a sufficient quantity of liquid. It is generally used alone but sometimes included in combinations (sorbitol, citrate, liquid paraffin = liquid petrolatum). Psyllium seeds may also be used in the adjunctive therapy of the painful component of spasmodic colitis.

All preparations based on plantains are contraindicated in case of pyloric stenosis. They are to be used with caution in case of megacolon by alteration of colon motility. The common recommendation against administering these products to bedridden patients is aimed (as is the administration of water) at avoiding product stagnation in the esophagus. It is best to avoid administering psyllium or ispaghula simultaneously with other medicines (to avoid affecting their absorption).

Note: French government information for the medical profession and for the public on laxative herbal remedies—bulk laxatives

The French Explanatory Note (1998) includes, for "laxative herbal remedies", "precise information for the medical profession and for the public". For psyllium, ispaghula, and all other bulk laxatives (e.g., algae, gums), this information is detailed in Annex IV, beginning with section 4.3 (p. 77 *sq.*). The Note also lists the elements

---

* The German Commission E monograph specifies that the use of *P. ovata* is contra-indicated in patients whose diabetes is difficult to control and that diabetic patients who use insulin may need to reduce the dose.

** The Latin name of psyllium is rarely mentioned in dietetic or clinical publications. When it is mentioned, it appears that in English, the terms "psyllium" or "plantago seeds" correspond sometimes to *P. psyllium*, sometimes to *P. ovata*, in other words ispaghula. The United States Pharmacopoeia (XXII) includes, in the same "Plantago seeds" monograph, *P. ovata*,

* In the United States, the FDA allows foods containing psyllium (Indian psyllium) soluble fibers to make health claims on reducing the risk of coronary heart disease when such foods are part of a a low saturated fat, low cholesterol diet. Ref. FDA Talk Paper http://vm.cfsan

that are required on the label (*ibid.*, p. 79 sqq.). After a reminder that the medicine is recommended for constipation, the document lists:

• the cases in which the medicine is not to be used ["certain ailments of the intestine and colon; in cases of abdominal pain (stomach ache)]. Although this wording is vague*, the recommendation is completed by the phrase, "if in doubt, it is essential to obtain the advice of your doctor or pharmacist";

• special warnings on occasional and chronic constipation. In the former case, there is a reminder that "any recent constipation not explained by a change of lifestyle" (e.g., travel), "and any constipation accompanied by pains, fever, or swelling of the belly, should be referred to a doctor for advice". In the latter case, the Note offers a reminder of the possible origins of prolonged constipation, then lists what the treatment may include: "an increase in the proportion of vegetable products in your diet (green vegetables, salad, wholemeal bread, fruit...); an increase in consumption of water and fruit juices; an increase in physical exercise (sports, walks,...); training to re-establish the normal reflex of bowel evacuation; sometimes, adding bran to your diet". The case of children is the topic of a special paragraph that emphasizes "hygiene measures and diet" and discourages the prolonged use of laxatives;

• "precaution for use", particularly the need to drink plenty of fluids during treatment;

• the risk of drug interaction and the need to inform the doctor or pharmacist of any other ongoing treatment;

• the need for pregnant women to seek medical advice** before using laxatives (or before continuing to use them);

• advice on use (do not increase doses, do not prolong use without medical advice);

• possible adverse effects: abdominal meteorism (flatulence).

• PSYLLIUM,
P. afra L. (= *P. psyllium* L.), *P. indica* L. (= *P. arenaria* Waldst. & Kit.)

The ripe, whole, and dried seeds of these two species are listed in the 3rd edition of the European Pharmacopoeia.

The Plants, Composition. These plantains are small size annual herbs with erect stems and with opposite or verticillate leaves devoid of differentiated petiole. The inflorescences are slender spikes with short bracts (*P. afra*), or tight spikes with acute bracts that are longer than the flowers (*P. indica*). The fruit is a circumscissile capsule with two ovoid and flattened seeds. Plantains grow in sandy regions of the Mediterranean basin and are cultivated in Provence (*P. afra* = *plantain noir de Provence, plantain des sables, plantain d'Italie* in French), in Spain, and in Morocco (*P. indica*).

The seed contains 5-10% lipids with unsaturated fatty acids, sterols, proteins (15-18%), traces of cyclopentanopyridine-type alkaloids, aucubin (an iridoid), and carbohydrates: planteose, a trisaccharide, and 10-12% mucilage of the heteroxylan type which yields upon hydrolysis D-xylose (70%), L-arabinose (10%), α-D-galacturonyl-(1—>4)-L-xylose, and D-galactose.

The Drugs. They consist of the seeds. That of *P. afra* is smooth, shiny, elliptical (2-3 x 0.8-1 mm), enlarged at one end, and its color ranges from light brown to blackish-brown; the underside has a linear groove with ridges on both sides and with a spot of lighter color in the middle. The *P. indica* seed is practically identical, a little less shiny, and larger (maximum 1.5 mm).

Tests. The French official drug contains not more than 1% foreign elements, including unripe greenish seeds. The absence of seeds of other plantain species must be verified, especially seeds with a central, dark spot on the groove (*P. lanceolata* L., *P. major* L.), and seeds that present external gray-brown or pinkish surfaces (*P. sempervirens* Crantz, *P. ovata* Forsk). The swelling index is not less than 10.

• ISPAGHULA,
Plantago ovata Forssk. (= *P. ispaghula* Roxb.)

According to the European Pharmacopoeia (3rd edition, 1999 add.), the drug consists of the seed or the seed tegument. Ispaghula is an annual plant cultivated in India and Pakistan that adapts readily to western Europe. The stem is very ramified and bears linear leaves that are lanceolate, dentate, and pubescent. The flowers are white and grouped into cylindrical spikes. The seed is oval (1.5-3.5 x 1.5-2 x 1-1.5 mm), smooth, and pinkish-beige; its convex side is clearly carinate and has a light brown spot as long as about one quarter of the total length of the seed. The tegument powder consists of episperm fragments with mucilage-filled cells and internal tegument fragments with brownish cells; in addition, the seed powder contains albumen fragments (containing aleurones and oil) and starch grains. The swelling index is not less then 9 (seed) or not less than 40 (tegument).

Many elements have been identified in the seed: proteins, lipids, sterols, triterpenes, and aucubin glycoside. The mucilage level is substantial and can reach 30%. This mucilage is chiefly constituted (85%) of a soluble polysaccharide fraction dominated by D-xylose. The polymer backbone is a xylan with 1—>3 and 1—>4 linkages with no apparent regularity in their distribution. The monosaccharides in

* The "summary of characteristics" is more detailed: "intestinal obstruction or partial obstruction, abdominal pains of unknown cause, faecal impaction".

** The same "summary of characteristics" states that monitoring pregnant women who take

OTHER PSYLLIUM

• GREAT PLANTAIN, *P. major* L., BUCKHORN PLANTAIN, *P. lanceolata* L.

In January 1996, a monograph was added to the French Pharmacopoeia for the dried leaf of great plantain and the dried leaf of buckhorn plantain, two species native to France. The aucubin content (determined by HPLC) is not less than 0.2% for the great plantain leaf and not less than 0.5% for the buckhorn plantain leaf. *P. lanceolata* is also official in Germany (DAB 10).

The common subspecies of great plantain (subsp. *major* and subsp. *intermedia* (DC) Arcangeli, see Flora Europea) and buckhorn plantain are perennial plants with whorled leaves. The blade is either oval and sinuate, narrowing abruptly into a winged petiole (*P. major*), or elliptical (*P. intermedia*), or lanceolate, or acute at the apex and narrowing at the base into a slender petiole (*P. lanceolata*). The flower spikes are cylindrical or ovoid and are on non-ramified stems.

The chemical composition of the different species is not known with any precision. The great plantain leaf comprises iridoids and phenols: flavonoids, phenolic acids, and phenylpropanic esters of glycosides (verbascoside, plantamajoside = purpureaside A). The literature available on *P. lanceolata* shows that its composition is rather similar: iridoids (aucubin [0.3-2.5%], catalpol [0.3-2.1%], asperuloside), flavonoids, phenolic acids, and mucilage (6-7%) rich in D-galactose, L-arabinose, and containing nearly 40% uronic acids. *P. major* seeds provide a mucilage similar to that of other species in the genus (araboxylan rich in uronic acids).

The identification of the drug is based on a microscopic examination of the leaf powder and on the TLC of a methanol extract. The microscopic examination shows, among others, the presence of two types of trichomes: covering trichomes, pluricellular, long (200 µm in *P. major*) or very long (800 µg in *P. lanceolata*); the glandular trichomes have a unicellular stalk and a bicellular head (30 µm, *P. major*) or pluricellular head (100 µm, *P. lanceolata*). TLC analysis reveals the presence of aucubin in both species and of catalpol in buckhorn plantain (visualization by heating after spraying with phloroglucinol and hydrochloric acid).

The pharmacology of these species remains unexplored. Note, however: 1. the protective and water-retaining role of the hydrocolloid, and 2. the potential role of iridoids in antiinflammatory activity (recognized for catalpol derivatives). Extracts prepared without heating are believed to be antibacterial *in vitro*. In France, the plantain leaf is only used topically. It is (French Expl. Note, 1998) traditionally used as an adjunctive, emollient, and antipruriginous treatment of dermatological conditions, as a trophic protective agent for cracks, abrasions, frostbites, chaps, and insect bites, and for eye irritation or discomfort of various etiologies (for example smoky atmospheres, eye strain, seawater or swimming pool water). The German Commission E monograph describes uses by the oral route for catarrh of the respiratory passages and to treat inflammation of the mouth and throat; it is also used topically for inflammation.

B. Polysaccharides of Malvales

The species of the different families that constitute this Dilleniidae order very often contain mucilaginous cells or canals. Pharmacy and phytotherapy use Malvaceae very commonly (high mallow, marshmallow), Tiliaceae (Lime tree), and Sterculiaceae (see above: karaya gum). Other families in this order are only of limited interest to pharmacy or industry, and not necessarily used for their polysaccharides: Bombacaceae (baobab [*Adansonia* sp.] and kapok tree [*Ceiba* sp.] family), Bixaceae (annatto tree [see carotenoids], kutira gum), Cistaceae, Elaeocarpaceae, and more.

• HIGH MALLOW, *Malva sylvestris* L., MARSHMALLOW, *Althæa officinalis* L., Malvaceae

Marshmallow dried root and dried suber-free root, whole or in fragments, is described in the 3rd edition of the European Pharmacopoeia. The dried leaf, the dried flower, and the dried suber-free root of marshmallow, as well as the dried flower of high mallow (or its cultivated varieties), are the subject of a monograph in the 10th edition of the French Pharmacopoeia.

The Plants, the Drugs.

• Marshmallow is a tall (0.6-1.2 m) perennial herb, with lobate and dentate leaves that are tomentose on both sides. The flowers are pentamerous and include a calyculus with 6-9 divisions fused at the base and shorter than the calyx; the corolla has five pinkish-white petals emarginate at the top; the stamens are numerous and fused by their filament. The species grows wild in all of Europe, mainly in damp areas of the Atlantic seaboard. The root is odorless and of bland taste, and consists of whitish conical sticks (10-15 x 1-2 cm). The microscopic examination reveals cells in the parenchyma of all three drugs that stain readily with ruthenium red.

• The high mallow is a fairly polymorphous species close to the previous one, although smaller, and potentially perennial by subterranean buds. The stems are not very branchy and bear pentalobate leaves and flowers with a calyculus reduced to three free pieces, with cuneiform petals, emarginate, purplish with crimson veins, and with a staminodial tube covered with hairs growing in a star pattern. As is the previous one, this is a common plant which colonizes roadsides and shoulders in almost all of Europe. In the cultivated varieties, the number of elements ranges from 3 to 7 (calicle), from 5 to 8 (calyx), and from 5 to 10 (corolla). The flower can be two to three times larger than that of the wild species. The microscopic examination of the powdered flower reveals baseball bat-shaped glandular trichomes, and covering trichomes—some short, some sharply curved—either isolated or in star

Chemical Composition.

• All marshmallow organs contain mucilage. In the case of the roots, it has a highly ramified structure composed of D-galactose, L-rhamnose, D-glucuronic acid, and D-galacturonic acid. Globally, Malvaceae polysaccharides have a close structural similarity to pectin polysaccharides: rhamnogalacturonic chain, and uronic acid and galactose branches.

The root contains, as do the leaf and flower, flavonoids (*O*-glycoside in the 8 position of hypolaetin and potassium salt of the *O*-glycoside in the 8 position of the 4' methyl ether of isoscutellarein sulfate). Phenolic acids and scopoletin have also been characterized.

• Although the structure of the polysaccharides, and of the glucuronates of flavones and flavonols of the high mallow leaf are fairly well known—they are, as in the marshmallow, derivatives that are 5,7,8-trisubstituted on the A ring—little is known of the composition of the flower: flavonoids, anthocyanins (some zwitterionic), polysaccharides, and more.

Tests.

• marshmallow. The mucilage content is determined gravimetrically by weighing the precipitate obtained by dilution with ethanol of a concentrated aqueous extract of the drug. The weight of the dried precipitate must be >8% (flower) or >10% (leaf) of the dried drug weight. A search for potential substitution of marshmallow root by Solanaceae roots is required by alkaloid extraction and TLC analysis of the extraction residue.

• high mallow. The test includes a study of anthocyanins (by aqueous extraction in acidic medium, hydrolysis in a sealed tube, and characterization of the genins by TLC) and the determination of the swelling index (>15).

Properties and Uses. Pharmacological knowledge on these species is nonexistent. It appears that the only published data are about the immunogenic properties, studied *in vitro* and in the mouse, of the polysaccharide fraction of the marshmallow root* p. 113. The high mallow leaf and flower, and the marshmallow leaf, flower, and root are approved by the French Explanatory Note (1998) for the indication: "symptomatic treatment of constipation" and for the following indications, preceded by the phrase "traditionally used":

- by the oral route: adjunctive therapy of the painful component of spasmodic colitis and symptomatic treatment of cough;

- topically:

1. adjunctive emollient and itch-relieving treatment of dermatological conditions, protective trophic in the treatment of cracks, abrasions, chaps, and insect bites,

2. antalgic in conditions affecting the buccal cavity, the oropharynx, or both (in collutoria or lozenges).

High mallow is also traditionally used locally in cases of eye irritation or swimming pool water). Another Malvaceae, hollyhock (*Althaea rosea* L., flower, leaf), is approved in France for the same indications as high mallow and marshmallow (except for constipation). Flowers of high mallow and marshmallow are used in the composition of cough teas**.

• LIME TREE or linden tree, *Tilia cordata* Mill., *T. platiphyllos* Scop., *T.* x *vulgaris* Heyne, Tiliaceae

The two *Tilia* species and their hybrid can be found in the 3rd edition of the European Pharmacopoeia: the monograph specifies that the drug consists of the whole dried inflorescence of any one of these species or the mixture of both. The flowers and bracts have been available over the counter for a long time and they are used to prepare infusions that would be slightly sedative. Pharmacy also uses lime tree sap-wood (*aubier de tilleul* in French) defined by the 10th edition of the French Pharmacopoeia as "the bark partially freed of suber [...] reduced to fragments of variable size [...] it corresponds to the detachable bark together with the wood of that year, that is the zone where the sap circulates, from the suber on the outside to the older wood on the inside."

---

* The rhamnogalacturonan from marshmallow root inhibits the cough reflex induced in the cat by a mechanical stimulus (*per os*, 50 mg/kg): see Nosalova, G., Strapkova, A., Kardosova, A. and Capek, P. (1993). Antitussive Activity of a Rhamnogalacturonan from the Roots of *Althaea officinalis*, var. *robusta*, *J. Carbohydrate Chem.*, **12**, 589-596.

** "Cough teas are used to prepare infusions, decoctions, and other analogous preparations. They are obtained by mixing dried plants or parts of plants that are peeled, incised or pounded, then freed of dust. Salts are sometimes added. The preparation must be sufficiently homogeneous." Cough teas consist of an equal weight mixture of capitulums of cat's foot and coltsfoot, of violet, high mallow, and marshmallow flowers, and of poppy and mullein petals. Virtually nothing is known of cat's foot (*Antennaria dioica* Gaertn. = *Gnaphalium dioicum* L., Asteraceae), other than the fact that it contains ordinary flavonoids, that it stimulates phagocytosis by the reticuloendothelial system, and that it is approved in France as "traditionally used" for the symptomatic treatment of cough (oral route) and as antalgic in diseases of the oral cavity, of the oropharynx, or of both (collutoriums, lozenges). Coltsfoot is considered by some authors as a mucilage-containing drug, and it also contains alkaloids (see pyrrolizidines, p. 842). The violet (dried flower of *V. lutea* Huds. [European yellow violet], *V. calcarata* L., or *V. odorata* L. [common violet],Violaceae), is traditionally used in the symptomatic treatment of cough and externally as an adjunctive, emollient, and antipruriginous treatment. The poppy contains traces of alkaloids (see isoquinolines, p. 919). Mullein (*Verbascum thapsus* L., *V. densiflorum* Bertol., *V. phlomoides* L., Scrophulariaceae) is hard to classify; the indications for which it is approved in France (the same as for high mallow and marshmallow, plus mouthwashes) lead us to discuss it here because of its mucilage. Indeed the flowers contain approximately 3% polysaccharides comprising uronic acids, galactose, and arabinose. They also contain flavonoids, phenylpropanic glycoside esters, saponins, iridoids (aucubin, catalpol and derivatives), and lignan glycosides (see Warashina, T., Miyase, T. and Ueno, A. (1992). Phenylethanoid and Lignan Glycosides from

TILIA CORDATA Mill.

The monograph specifies that this sap-wood may come from the two species above, but also from *T.* x *vulgaris* Heyne and from *T. sylvestris* Desf. *

The Plant, the Drug. The taxonomy of the genus is delicate and encumbered by numerous synonyms and pointless descriptions of species and varieties: often these are only hybrids, and all European species are interfertile. The most common species are:

- the Lime tree (*T. cordata* Mill. = *T. parvifolia* Ehrh. ex Hofm.);
- the broad-leaved lime or big-leaf linden, *T. platiphyllos* Scop., for which the Flora Europea describes three subspecies: subsp. *platiphyllos*, subsp. *cordifolia* (Besser) C.K. Schneider and subsp. *pseudorubra* C.K. Schneider;
- the hybrid of the previous ones: *T.* x *vulgaris* Heyne (= *T.* x *europaea* L. = *T. intermedia* DC = small-leaved lime).

Another species, the silver linden (*T. tomentosa* Moench = *T. argentea* DC.), is also common, but may not be considered for any medicinal use (its flowers, as those of *T. americana* L., are hexamerous).

Lime trees are tall trees with smooth gray bark, with leaves that are cordate at the base and abruptly acuminate, smaller (3-9 cm) for *T. cordata* than for *T. platiphyllos* (6-9 [12] cm). The flowers are pentamerous, pleasantly fragrant, and grouped in cymes of 2 to 7 (16) flowers with sepals that are easy to detach, and with spatulate, thin, and finely veined petals. The stamens are free and generally gathered in five groups. On the inflorescence axis is a linguiform bract, membranous, greenish-yellow, and fused onto the axis, about half way up its median vein. The fruit is a small indehiscent capsule of 6-8 (10) mm.

The inflorescences are collected manually when almost all of the flowers are in bloom. On the market there are a lot of Lime tree flowers from distant sources (presumably *T. chinensis* Maxim., *T. mandschurica* Rupr.) and of very uneven quality (especially the "tea bag" cuts).

Chemical Composition. Lime tree inflorescences or linden flowers are rich in phenolic compounds: phenolic acids, proanthocyanidins (B-2, B-4), tannins, and especially flavonoids (1%: quercitrin, tiliroside [*p*-coumaroyl-6"-glucosyl-3-kaempferol], hyperoside, rhamnosyl-7-kaempferol, and more). Their odor is linked to a small amount of essential oil, which varies in composition with the localization: that from bracts is rich in phenylacetaldehyde and other aldehydes, whereas that from flowers is dominated by monoterpenoid hydrocarbons. Both contain oxygenated mono- and sesquiterpenes (for example, linalool, geraniol, farnesol, free and acetylated, camphor, carvone, cineole), aromatic alcohols (phenylethanol, benzylic alcohol, and more), phenols and alkanes. The drug also contains a mucilage composed of five fractions dominated by D-galactose, L-arabinose, L-rhamnose, and uronic acids.

* Commonly considered to be synonymous to *T. cordata* Mill. …

The composition of lime tree sap-wood is ill-known (phenolic acids, tannins, fraxoside, esculoside, amino acids, and more); several authors report, with no reference, the occurrence of phloroglucinol. French official lime tree sap-wood contains between 1.5 and 7% total polyphenols determined by measuring the absorbance of a decoction after reaction with phosphomolybdic acid.

Tests. The drug is identified by its macro- and microscopic characteristics (floral parts, tissues, pollen) and by TLC analysis of a methanolic extract, which shows numerous bands corresponding mainly to flavonoids and phenolic acids (visualization by aminoethanol diphenylborate and macrogol [=PEG] 400). The assay per se includes foreign matter (<2%). Hexamerous flowers (*T. americana* L., *T. tomentosa* Moench) are found only exceptionally. The absence of inflorescences whose bracts have stellate covering trichomes on the abaxial (i.e., ventral) face and whose corolla appears to be double because of petalaceous staminodes is verified.

Properties and Uses. The pharmacological potential of the flowers does not seem to have especially caught the attention of pharmacologists: although some terpenoid alcohols are not inactive (e.g., spasmolytic, sedative), note that the most recent studies did not find them in the batches investigated...

The sap-wood underwent several experimental studies in the early 1960s: it is a musculotropic spasmolytic (guinea pig duodenum), a serotonin antagonist, a diuretic, and a hypotensive agent. At the gall-bladder level, it decreases the flow rate of bile. In humans, some observations support the potential usefulness of sap-wood preparations for biliary dyskinesia.

Linden flowers are essentially used, as are a number of other so-called medicinal plants, for the preparation of "hygienic and comforting beverages". They may enter in the composition of plant-based medications by claiming the following indication: "traditionally used in the symptomatic treatment of neurotonic states in adults and children, especially for minor sleep disturbances". Topically, linden flower preparations are used as an adjunct in the emollient and itch-relieving treatment of dermatological conditions, and as a trophic protective agent for cracks, abrasions, frostbites, chaps, and insect bites (French Expl. Note, 1998). The German Commission E monograph attributes to linden flowers diaphoretic properties (literally, to carry through, i.e., facilitates the secretion of humors). Package labels are required to mention the relief of throat irritation during catarrh of the respiratory tract, colds, etc. for which a sweat cure is desired.

Linden sap-wood is traditionally used by mouth to facilitate urinary and digestive elimination functions, as a choleretic and cholagogue, and to facilitate the renal elimination of water.

Phloroglucinol and its trimethyl ether are proposed, orally or by injection, as spasmolytic agents for hepatic or nephritic colic, spasmodic colitis, spasmodic dysmenorrhea, and more.

C. Other Mucilage-containing Drugs

• Flax, *Linum usitatissimum* L., Linaceae

The Plant. Flax is an annual erect herb with simple leaves that are alternate and lanceolate. The pentamerous blue flowers stand solitary on slender ramifications of the stem. The fruit is a capsule with ten 1-seeded locules. "Fiber" flax varieties have been cultivated in Europe since ancient times. Nowadays the so-called "seed" varieties are exploited (Canada, China, India). They have multiple flowers on ramified stems. They are shorter plants, therefore they are less vulnerable to being beaten down by the wind. In France, it is mostly fiber flax that is cultivated. In the early 1980s, world production was in the neighborhood of 3 million metric tons.

The Drug. Flaxseed or linseed, dried and ripe (Eur. Ph., 3rd Ed.), is elongated, ovoid, flattened (4-6 x 2-3 x 1.5-2 mm), and rounded at one end. Its tegument is dark reddish-brown, smooth, shiny, and its surface finely punctuated (as seen through a magnifier). The external walls of the epidermis are mucilaginous. The swelling index of the drug is greater than 4, and that of the powdered drug greater than 4.5.

Chemical Composition. Linseed contains oil (35-45%), proteins (20-25%), and mucilage (6-10%); of note is the occurrence of cyanogenic glycosides (linustatin, neolinustatin, traces of linamarin), of a glycoside of secoisolariciresinol, and of phenylpropanic glycosides. The mucilage can be fractionated into a neutral fraction—a ramified arabinoxylan composed of D-xylose, L-arabinose, D-glucose, and D-galactose—and an acidic fraction mainly composed of L-rhamnose and D-galactose.

Linseed oil is a highly unsaturated oil, therefore the ground seeds spoil in storage (oleic acid, 10-18%; linoleic acid, 23-24%; α-linolenic acid, 35-50%).

Properties and Uses. The occurrence of mucilage justifies the use of linseed as a bulk laxative [French Expl. Note, 1998]. The seeds must be taken with a sufficient quantity of fluids to avoid any risk of obstruction of the digestive tract. Folk medicine traditionally mixes linseed powder (in French *farine de lin* or linseed *meal*) and mustard seed powder to manufacture cataplasms (efficacious? revulsant!). The German Commission E monograph acknowledges that the drug is capable of increasing the volume of the bowel contents, therefore it stimulates peristalsis, and it protects the mucous membrane in case of inflammation (colitis). Obese patients are advised to swallow the seeds without chewing them, to avoid releasing the oil, a source of calories (1 g of seeds = 4.7 kcal).

The occurrence of cyanogenic glycosides does not preclude the consumption of the seeds. Although these are not food, they are approved in France, as long as their assessment of the *Conseil supérieur d'hygiène publique de France* was that, under these conditions, they have no deleterious health effects.

The hormonal symptoms observed during the menstrual cycle in women who consume linseed daily have been attributed to phyto-estrogens, namely enterodiol and enterolactone. These compounds are thought to arise from the degradation, by the flora of the colon, of the glycoside of secoisolariciresinol. They are lignans which exert, at least in experimental conditions in animals, an antitumor effect (e.g., decrease in tumor induction by benzanthracene).

Recently, it was shown that adding linseed to animal feed yields food products (eggs, meats, fish) enriched in fatty acids of the *n*-3 series.

Fibers. Recall that flax fibers are obtained by retting (i.e., by fermentation in heaps for three to eight weeks, to degrade hemicelluloses), crushing, and separating. Next the fibers are bleached to increase their cellulose content and used by the textile industry, as well as to obtain non-resorbable surgical threads (sterile flax suture, Eur. Ph., 3rd Ed.). Green flax (not retted) is directly used in the paper industry (cigarette paper, special papers); the residues have uses similar to those of hemp.

• Quince, *Cydonia vulgaris* L., Rosaceae

The seeds of this cultivated tree provide a mucilage used in the formulation of cosmetic products. The fruits are edible; they supposedly exert an antidiarrheal effect due to the tannins that they contain.

Other drugs probably owe their activity in part to the presence of a polysaccharide fraction: this may be the case for comfrey root, which folk medicine considers to be emollient and healing, and this is probably also the case for aloe gel (see anthraquinone chapter, p. 436).

5. PECTINS

Generalities. Pectins may be defined as a group of polymers built around 1—>4-linked α-galacturonic residues associated with arabinan and galactan units. They are glycanogalacturonans in which the nature of the monosaccharides linked to galacturonan varies with the botanical origin. The structure of the polymer also varies, for a given source, depending on the growth stage. Pectins are chiefly localized in the middle lamella of the vegetable cell wall (except in Poaceae) where they are associated with cellulose and hemicelluloses by linkages whose nature remains to be determined. These polymers are particularly abundant in unripe fruits: at first they are insoluble and impart a certain rigidity to the tissues; later they are

Commercially and traditionally, pectic acids with carboxylic functions that are not (or almost not) methylated are distinguished from salts or pectates. The term pectinic acid is reserved (as is that of pectinates) for partially methylated derivatives. Practically, pectins are classified in function of their *degree of methylation* (DM), also called *degree of esterification* (DE). The DM of pectic acids is less than 5, for a DM up to 50 pectins are deemed weakly methylated, and above 50, pectins are called highly methylated. Pectins, as the majority of polysaccharides, have a range of formulas and origins. Their structure and consequently their properties depend on the source, the isolation procedures, and the post-extraction treatments.

Structure of pectin polysaccharides. Currently, homogalacturonans are known (for example in the capitulum of sunflower) and so are rhamnogalacturonans. The former are rare, as their name indicates they consist of a 1—>4-linked α-D-galac-turonic acid chain, and they are highly methylated. Rhamnogalacturonans, on the other hand, have a main chain interrupted by α-L-rhamnose units linked as follows:

—>4)-β-D-Gal*p*A-(1—>2)-β–L-Rha*p*-(1—>

It appears that there exists, depending on the source, polymers with purely galacturonic regions interrupted without regularity by rhamnoses, and others in which the alternating pattern of rhamnose and galacturonic acid repeats itself over segments of variable length. In most cases, the main chain is substituted by oligosaccharides rich in arabinose and in galactose linked (mostly) on the C-4 of the rhamnose-containing residues on the chain. Most often the polymer appears to be a macromolecule with alternating non-substituted segments (smooth zones) and segments with numerous lateral chains (hairy zones).

Schematically, the characteristic element—and the determining factor in terms of rheological behavior—is that rhamnose units cause a discontinuity in the linearity of the polymer: they form pectic elbows that delineate zones that will allow junctions, i.e., gelification, but not precipitation.

Production of Pectins. Industrial pectin extraction starts from citrus waste (2.5-4% of the fresh pulp weight) and apples (0.5-1.6% of the fresh weight), in other words from the residual pulp leftover from manufacturing fruit juices. Pectins also occur in large quantities in sugar beet pulp (see p. 30) but their gelifying properties are not optimal. The products generally have a high DM (70-75); if necessary they are partially deesterified. After inactivating the enzymes by boiling—it is also possible to start from carefully dehydrated material—pectin is dissolved in hot acidic aqueous solutions. The extract, filtered or centrifuged, and if needed freed from starch (by digestion by amylases), is treated with isopropanol: pectin precipitates. The precipitate is filtered, dried, and ground. The temperature, pH, and duration of acidic treatment determine the final DM. Partial amidification is also possible. In theory, other sources of pectin may be used: carrot, sunflowers, beet pommace, but in this case the high degree of acetylation of the polymer prevents intermolecular bonds and makes artificial means necessary to cause gelification.

Properties. Pectic acid is insoluble in water but its solubility in water increases with the DM. Alkaline pectates are soluble in water, whereas pectates of di- and trivalent cations are sparingly or not at all soluble. Pectin solutions are very viscous and their behavior is pseudoplastic: the carboxylic groups of the polyanion are ionized, the molecules repulse one another, their conformation is extended, they are highly hydrated, and they remain independent.

In specific conditions, solutions prepared hot gel upon cooling. The structure of pectins of low DM is not without similarity to that of alginic acid: the rhamnose molecules (the pectic elbows) play the role of the poly-M sequences, and the poly-galacturonic sequences act like poly-G sequences. Gelification occurs rapidly, in the presence of calcium, by formation of junction zones of the egg-box type.

In the case of pectins of high DM, gelification takes place slowly in acidic medium and in the presence of sucrose: the acidity decreases the dissociation of the residual carboxyls (and therefore the intermolecular repulsion) and the sucrose "fixes" the water which normally hydrates the polymer, thus favoring the polymer-polymer interaction over the polymer-solvent interaction and consequently the formation of a three-dimensional array, mainly through hydrogen bonds.

Uses of Pectins. Pectins are of interest in pharmacy above all because of their hydrophilicity: by absorbing the water, they act as a thickening preparation on the gastric contents and regularize transit; they ferment fairly rapidly and enhance bacterial growth, therefore they increase the feces volume. They are used for the symptomatic treatment of vomiting in the infant, and for diarrhea.

In dietetics, the regular use of pectins has proved efficacious in the control of blood cholesterol levels and the prevention of cardiovascular diseases (on these properties of soluble fibers, see guar gum [p. 101] and in the previous chapter, dietary fibers, p. 79).

Useful in pharmaceutical technology, pectins are mostly used in food technology as stabilizers and gelifiers (Eur. id. code E440a [pectins] and E440b [amidated pectins]) in jams, jellies, candies, frozen desserts, and sauces.

6. BIBLIOGRAPHY

Generalities

Coppen, J.J.W. (1995). Gums, Resins and Latexes of Plant Origin, (Non-wood Forest Products, n° 6), FAO, Rome.

Haskell, W.L., Spiller, G.A., Jensen, C.D., Ellis, B.K. and Gtaes, J.E. (1992). Role of Water-soluble Dietary Fiber in the Management of Elevated Plasma Cholesterol in Healthy Subjects, *Am. J. Cardiol.*, **69**, 433-439.

Jensen, C.D., Spiller, G.A., Gates, J.E., Miller, A.F. and Whittam, J.H. (1993). The Effect of Acacia Gum and a Water-soluble Dietary Fiber Mixture on Blood Lipids in Humans, *J. Am. Coll. Nutr.*, **12**, 147-154.

McNamee, B.F., O'Riordan, E.D. and O'Sullivan, M. (1998). Emulsification and Micro-encapsulation Properties of Gum Arabic, *J. Agric. Food Chem.*, **46**, 4551-4555.

Menzies, A.R., Osman, M.E., Malik, A.A. and Baldwin, T.C. (1996). A Comparison of the Physicochemical and Immunochemical Properties of the Plant Gum Exudates of *Acacia senegal* (Gum Arabic) and *Acacia seyal* (Gum Tahla), *Food Addit. Contam.*, **13**, 991-999.

Phillips, G.O. (1998). Acacia Gum (Gum Arabic): a Nutritional Fibre; Metabolism and Calorific Value, *Food Addit. Contam.*, **15**, 251-264.

Stack, P.E. and Thomas, E. (1995). Pharmacobezoar: an Evolving New Entity, *Dig. Dis.*, **13**, 356-364.

Whistler, R.L. and BeMiller, J.N. (1993). Industrial gums, 3rd ed., Academic Press, New York.

Guar

Groop, P.-H., Aro, A., Stenman, S. and Groop, L. (1993). Long-term Effects of Guar Gum in Subjects with Non-insulin-dependent Diabetes Mellitus, *Am. J. Clin. Nutr.*, **58**, 513-518.

Konjac

Arvill, A. and Bodin, L. (1994). Effect of Short-term Ingestion of Konjac Glucomannan on Serum Cholesterol in Healthy Men, *Am. J. Clin. Nutr.*, **61**, 585-589.

Doi, K. (1995). Effect of Konjac Fibre (Glucomannan) on Glucose and Lipids, *Eur. J. Clin. Nutr.*, **49**, suppl. 3, S190-S197.

Wu, J. and Peng, S.-S. (1997). Comparison of Hypolipidemic Effect of Refined Konjac Meal with Several Common Dietary Fibers and their Mechanisms of Action, *Biomed. Environ. Sci.*, **10**, 27-37.

Fenugreek

Sharma, R.D., Sarkar, A., Hazra, D.K., Mishra, B., Singh, J.B., Sharma, S.K., Maheshwari, B.B. and Maheshwari, P.K. (1996). Use of Fenugreek Seed Powder in the Management of Non-insulin Dependent Diabetes Mellitus, *Nut. Res.*, **16**, 1331-1339.

Plantago spp.

Chan, E.K. and Schroeder, D.J. (1995). Psyllium in Hypercholesterolemia, *Ann. Pharmacother.*, **29**, 625-627.

Dadvidson, M.H., Dugan, L.D., Burns, J.H., Sugimoto, D., Story, K. and Drennan, K. (1996). A Psyllium-enriched Cereal for the Treatment of Hypercholesterolemia in Children : a Controlled, Double-blind, Crossover Study, *Am. J. Clin. Nutr.*, **63**, 96-102.

MacMahon, M. and Carless, J. (1998). Ispaghula Husk in the Treatment of Hyper-cholesterolaemia: A Double-blind Controlled Study, *J. Cardiovasc. Risk*, **5**, 167-172.

Marteau, P., Flourié, B., Cherbut, C., Corrèze, J.-L., Pellier, P., Seylaz, J. and Rambaud, J.-C. (1994). Digestibility and Bulking Effect of Ispaghula Husks in Healthy Humans, *Gut*, **35**, 1747-1752.

Roberts, D.C.K., Truswell, A.S., Bencke, A., Dewar, H.M. and Farmakalidis, E. (1994). The Cholesterol-lowering Effect of a Breakfast Cereal Containing Psyllium Fibre, *Med. J. Aust.*, **161**, 660-664.

Sprecher, D.L., Harris, B.V., Goldberg, A.C., Anderson, E.C., Bayuk, L.M., Russell, B.S.,