

CHEMISTRY OF LEPROSY DRUGS^{1,2}

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PREFACE

In this review the history of the development of leprosy drugs up to 1904 has been touched upon only lightly, because scientific research upon the constitution of the natural drugs and the preparation of their derivatives can be said to date from that time. The reviewer has made no attempt to include all information on all medicinal products ever tested in one or more cases of leprosy; information of this nature may be found in a compendium such as Klingmüller's *Die Leprae*. He has, rather, attempted to include only that work which has had a definite influence on the progress made in this field of research. Some repetition has been unavoidable for the sake of clarity. He has conscientiously attempted to make this review international in scope but feels that there is probably much valuable material, either unpublished or unavailable, which might well be included. He will appreciate it if any such information will be forwarded to the editor of the JOURNAL at the earliest opportunity.

NATURAL PRODUCTS, CHAULMOOGRA GROUP

HISTORICAL

The first knowledge we have of the use of a special drug for the treatment of leprosy comes to us in the form of early Indian and Burmese legends dating before the time of Gautama. They relate tales of cures obtained by eating of the fruit and leaves of the *kalaw* tree which is the Burmese name for *Taraktogenos kurzii* King from which, we now know, is obtained the true chaulmoogra oil. Sen (49) states that there is mentioned in the medical part of the Ayurveda "Susruta" and "Bagvat" (100-900 A. D.) a *tubarak* oil for the treatment of leprosy. He believes that this oil was a hydnocarpus oil. According to Joseph (46), the efficacy of *Hydnocarpus wightiana* oil as a "blood purifier" was known to the Ayurvedic school of medicine many centuries ago, and it appears as the principal ingredient in the various prescriptions handed down by the Rishes of old for the treatment of skin diseases in general and of leprosy in particular.

The earliest mention of the use of chaulmoogra oil in the treatment of leprosy in China was by Chu Tan-Chi in the 14th century. He, however, disapproved of this remedy on account of its ill after-

effects. The Pen T'sao Kang Mu (The Great Herbal), a Chinese medical classic compiled by Li Shi-Chen during the years 1552-1578 and published in 1595, describes and gives a wood-cut of the seeds of *lu-braco* (probably *H. anthelmintica*) from Siam, as being effective in cases of leprosy. It gives directions for the separation of the oil and the preparation of pills. Towards the end of the 16th century this tree (*H. anthelmintica*) was introduced into China from Siam (49, 123).

In Japan chaulmoogra seeds were used as early as 1716. In China, successful use of the oil was reported by Hobson in 1855. The oil was apparently first imported for the treatment of leprosy in Hawaii by Bemiss in 1879. Shiga states that a Japanese physician, Goto, in Hawaii, used chaulmoogra oil subcutaneously about 1880. A Bengali physician, Monat, treated cases of leprosy with chaulmoogra oil about 1857. His results became known in Europe and were at least partially confirmed by numerous European physicians, among whom might be mentioned Bories, Danielssen, Hallepeau, Jeanselme, Roux and Tourtoulis.

In the meantime confusion reigned as to the source of the chaulmoogra seeds. According to Rock (94), they were thought to be those of a tree listed by Roxburgh in 1815 as *Chaulmoogra odorata*, but described by R. Brown under the name of *Gynocardia odorata*. Warburg figures the seeds of *T. kurzii* King as those of *G. odorata*. R. Br. Bories (6) introduced the drug into France but called it gynocardic chaulmoogra oil from the seeds of *G. odorata*. From his descriptions of the seeds, however, it is certain that he was dealing with true chaulmoogra oil and not a gynocardia oil. In 1899, G. Despres, a French pharmacist, discovered that the seeds of *T. kurzii* King were not those of *G. odorata*. He classified them under another species of this genus which he named *G. prainii*. However, this was a mistake as the seeds were not those of a gynocardia. Shortly afterwards Watt, the reporter on economic products of India, had plants of the purported source of chaulmoogra oil collected from the Kasalong forests of the Chittagong Hill tracts and sent them to Col. Prain, director of the Botanical Survey of India, for identification. Prain (91) in 1901 finally identified it with a plant collected by S. Kurz in Pegu, Burma, which Kurz had erroneously regarded as *H. heterophylla* Bl., but which Sir George King described in 1890 as a species of *Taraktogenos* and named *T. kurzii* in honor of the collec-

tor. Thus was finally cleared up the confusion as to the real source of chaulmoogra oil.

Until 1904 nothing was definitely known concerning the constituents of these seeds. In that year Power and Gornall (90) determined the constituents of chaulmoogra seeds, isolated chaulmoogric acid and prepared several of its compounds. In the following year Power and Barroweliff (89) determined the constituents of the seeds of *G. odorata*, *H. wightiana* and *H. anthelmintica* and isolated hydnocarpic acid, a homolog of chaulmoogric acid. Barroweliff and Power (4) completed their exhaustive research on these oils in 1907 by publishing their work on the constitution of chaulmoogric and hydnocarpic acids.

The reader who is interested in the early history and use of chaulmoogra oil will find the bibliographies on this subject by Bories and Despres (6) and Read (93) very helpful.

CHAULMOOGRA-GROUP PLANTS

Chaulmoogra-group oils are obtained from the seeds of certain trees of the order *Flacourtiaceae*, most of which belong to the genus *Hydnocarpus*. The seeds of these plants are supposed to contain chaulmoogric acid, and in most cases hydnocarpic acid.

The plants giving oils of this description are listed in Table 1, which gives an idea of the botanical relationship of these plants to one another. There is some question among botanists whether or not *Taraktogenos* can be kept as a separate genus distinct from *Hydnocarpus*. The main point of difference between the two genera are that *Hydnocarpus* has usually 5 sepals, 5 free petals and 5 stamens while *Taraktogenos* has usually 4 sepals, 4 or 8 petals and stamens 12 to numerous. Some species have been described which seem to be intermediate (e. g. *H. ilicifolia*). If it be ultimately found that no line of demarcation can be drawn, then *Taraktogenos* must be merged in *Hydnocarpus* (47, 60).

The information available on some of these plants is very slight. As time goes on the list of plants containing these acids will no doubt be considerably enlarged. The information at present available on each species is here given in the order of Table 1, which is arranged alphabetically rather than according to importance.

TABLE 1.—Summary of "chaulmoogra-group" oil plants

Flacourtiaceae ...	Hydnocarpaceae ..	Asteriastigma	macrocarpa
		Hydnocarpus	alcalae alpina anthelmintica castanea cauliflora curtisii dawnensis heterophylla hutchinsonii ilicifolia inebrians octandra ovoidea setumpul subfalcata venenata verrucosa wightiana woodii
	Oncoba	Taraktogenos	calvipetala integra kurzii microcarpa serrata
		Carpotroche	amazonica brasiliensis grandiflora integrifolia longifolia
		Oncoba	bracchiantera echinata glauca welwitschii

FAMILY HYDNOCARPACEAE

Asteriastigma macrocarpa is native to southern India. It has been reported from Madras, Travancore and Hindustan. It is said to have been found also in Burma. Both fruit and seed are larger than most species of *hydnocarpus*; it is known as the cannon ball tree. The fruit is spherical, about 13 centimeters in diameter. Except in size, both the fruit and seeds resemble those of *T. kurzii*.

The oil contains chaulmoogric or a mixture of chaulmoogric and hydnocarpic acids, also oleic acid (7 per cent) and a saturated acid, possibly palmitic. Perkins states that the oil is similar to that of *H. alcalae*, with almost as high a freezing point. On fractionation of the ethyl esters, the first fraction gives chaulmoogric instead of hydnocarpic acid. This would indicate the presence of little if any of the latter (2, 77, 78, 94).

Hydnocarpus alcalae is found in the province of Albay, island of Luzon, Philippine Islands, where it is called dudóa or dudu-dudu by the natives. The fruit is even larger than that of *A. macrocarpa*, but not spherical in shape, being about 20 centimeters long and 10 to 12 centimeters in diameter. The seeds are about 4 centimeters long by 2.5 centimeters wide. The fruit is best gathered in January and February. The seeds yield about 38 per cent oil. It is used by the natives in curing wounds. The free fatty acids from the oil contain approximately 90 per cent chaulmoogric acid and little or no hydnocarpic acid. The remainder is mostly palmitic acid with only traces of oleic acid (8, 27, 42, 85).

H. alpina is native to southern India and Ceylon. Wolff and Kolderwijn (122) in 1912 determined the physical constants of the oil and found them to agree rather closely with those of chaulmoogric oil. On the other hand, a Ceylon government report (42) states that chaulmoogric acid is present but hydnocarpic acid was not definitely detected, but may be present in small amounts (27, 42, 49, 122).

H. anthelmintica occurs abundantly in Siam (*luk krabao*), and in Cambodia, Cochin-China and Laos. It has also been reported from Burma. It is found in sandy loam river bottoms and in mountain valleys up to 1300 meters altitude. It grows to a height of 20-25 meters. It is estimated that there are enough trees along the Tachin and Pasak rivers in Siam to yield 200,000 kilograms of seeds annually. Rock states that there are now several thousand trees of this species growing in Hawaii. They have been cultivated also in Siam. The fruits usually ripen about August or September. The ripe fruits are more or less globular in shape and vary in size from 8 to 15 centimeters in diameter. The seeds are about the same shape and size as those of *H. wightiana* but have a smoother, thicker shell. The oil is used by the natives of Siam for cutaneous affections. The seeds form an article of export to China where they are known as Ta-fung-chi or Ta-feng-tzu. The oil is very similar to that of *H. wightiana* and *T. kurzii*. The seeds contain chaulmoogric, hydnocarpic, oleic and

palmitic acids and a very small amount of a cyanogenetic glucoside (47, 60, 85, 94).

H. castanea is a large tree not unlike *H. anthelmintica* but with larger leaves. It was first described from the Andaman Islands and since then has been recorded from Malacca, Perak, Burma (Martaban Hills) and Siam (on the peninsula only). The tree grows to a height of 25 to 30 meters, diameter of trunk up to 60 centimeters. The natives confuse it with *T. kurzii*, giving it the same native name, kalaw. The fruit, however, is quite different, being dark-brown, granular and rough in appearance, about the size of an orange. Although Rock states that the fruit is pointed at the apex, Kerr maintains that the mature fruit is not pointed but is globose in shape. A fruit contains about 20 to 30 seeds, closely packed, which gives them a polygonal form. The seeds take twice as long to germinate as do those of *T. kurzii*, probably because of their double testa. The Burmese use a decoction of the bark of the tree for internal disorders as well as for skin diseases. No data on authentic samples of oil from this tree can be found in the literature (47, 94).

H. cauliflora is native to Cotabato, Mindanao, Philippine Islands. The fruit, seeds and oil of this tree resemble those of *H. hutchinsonii* very closely (87).

H. curtisii was collected by Rock on the island of Penang. He states that this tree rarely grows over 5 meters tall. The fruits are small, about 2.5 centimeters in diameter and globose. No chemical examination has been made of the oil (94).

H. dawnensis occurs in Burma. The oil has been only recently analysed. It contains chaulmoogric and probably hydnocarpic acids (77).

H. heterophylla grows in the Dutch East Indies. The oil has been partially analysed; it contains both hydnocarpic and chaulmoogric acids (50).

H. hutchinsonii occurs in Zamboanga and Basilan, Mindanao, Philippine Islands. The tree grows to a height of 25 meters but it is usually not over 15 meters high. The fruits are globose, from 7 to 10 centimeters in diameter. They contain from 20 to 45 seeds in a small amount of pulp. The seeds are tightly packed in the fruit and hence have a polygonal shape about 2 to 2.5 centimeters long. The fruits are collected about July or August. The oil contains both hydnocarpic and chaulmoogric acids (85).

H. ilicifolia, also classified as *T. ilicifolia*, occurs more abundantly in Siam than any other species of *Hydnocarpus* or *Taraktogenos*. In one forest area of 1,650 square kilometers, it is estimated that there are more than 19,000,000 trees of this species. The species is dioecious and there are about two male trees to one female tree so only one third of the trees will bear fruit. The tree grows to a height of 20 meters, 1 meter in circumference. It is most abundant in the dry evergreen type of forest. The fruit is practically globose and of a very dark velvety brown, at a distance appearing black. It measures up to 5 centimeters in diameter and may contain from 4 to 26 seeds, the average being about 15. At present very little use is made of this tree. The seed oil is solid at ordinary temperatures. It contains both chaulmoogric and *hydnocarpic* acids (47, 94).

H. inebrians yields kanti oil which was used by a physician, Bhan Daji, in 1859 for the treatment of leprosy (49).

H. octandra occurs in Ceylon. It contains chaulmoogric acid and possibly a small amount of *hydnocarpic* acid (42).

H. ovoidea grows on the island of Samar, Philippine Islands. The very low optical rotation of the oil ($+0.7^\circ$) makes questionable its classification, chemically, as a chaulmoogra-group oil (87).

H. setumpul grows in the Dutch East Indies. The oil is rich in chaulmoogric acid but contains no *hydnocarpic* acid (50).

H. subfalcata occurs in Zambales, Pangasinan and Cagayan, island of Luzon, also in the islands of Samar and Mindanao (Surigao), Philippine Archipelago. It has many native names. The fruit ripens in May. It is from 1 to 4 centimeters in diameter, containing from 2 to 8 small seeds. The oil contains both chaulmoogric and *hydnocarpic* acids (85).

H. venenata occurs in Ceylon and is said to be found also in East and West Deccan of India and in Burma. The seeds are similar to those of *H. wightiana* but are smaller, and they have seven veins in the cotyledon instead of five. The oil contains both chaulmoogric and *hydnocarpic* acids (7, 27, 42, 85).

H. verrucosa occurs in Burma. Peacock and Aiyar have recently given some analytical data on the oil which would indicate its similarity to *H. wightiana* oil (77).

H. wightiana occurs abundantly in southwestern India. The tree grows to a height of 7 to 10 meters. The fruit measures 6 to 12 centimeters in diameter. The seed is about 2 centimeters long, with longitudinal grooves and a knob at the end. This species is one of

the most abundant and easily accessible of the hydnocarpaceae. The oil contains both chaulmoogric and hydnocarpic acids. It is very similar in composition to that from *T. kurzii* with, however, a higher content of the optically active fatty acids. It contains about 1.2 per cent lauric acid, and an unknown unsaturated acid and probably a lower homolog of hydnocarpic acid (13, 27, 78, 85, 89).

H. woodii occurs in north Borneo. The seed is similar to that of *H. hutchinsonii* and the oil to that from *T. kurzii*. Both chaulmoogric and hydnocarpic acids have been identified in the oil (43, 85, 87).

Taraktogenos kurzii, yielding the oil to which the name chaulmoogra properly belongs, is widely distributed in Burma. It is also found in Siam, in Eastern Bengal and Assam. *T. kurzii*, called by the Burmese kalaw, grows to a height of 15 to 20 meters, in dense forests, in loamy, sandy soil. The fruits are practically spherical, about 7.5 centimeters in diameter. They contain from 1 to 24 seeds with an average of 10. The seeds are smoother and larger than those of *H. wightiana*. The trees produce fruits irregularly. Bears are very fond of the fruit flesh and large numbers of them roam the forest in search of the kalaw fruits. Wild pigs and certain fish eat the seeds. The natives state that the pigs and fish then become poisonous, producing vomiting and nausea if eaten. Collecting the seeds is very dangerous on account of tigers, bears and other wild animals. The fruit ripens in June or July, falls in the rainy season and is usually no longer fresh when gathered. For this reason, and because both the seeds and the oil deteriorate more rapidly than those of *H. wightiana*, the chaulmoogra oil of commerce is apt to be quite rancid, with a high free fatty acid content. It is often adulterated, and other hydnocarpus oils are often sold as chaulmoogra oil. The oil contains both chaulmoogra and hydnocarpic acids as well as a small amount of palmitic and linolic acids. Linolenic acid may also be present (9, 27, 31, 47, 48, 49, 77, 85, 90, 91, 94).

Other species (*T. integra*, *macrocarpa* and *serrata*) occur in Indo-China, chiefly in Cambodia and Laos. *T. calvipetala* and *T. serrata* occur very locally in Siam (47).

FAMILY ONCOBA

Carpotroche brasiliensis occurs in Brazil in the States of Rio, Minas, Espiritu Santo, Bahia and Pianhy; also in Peru and Colombia. The Brazilian name is sapucainha. The tree grows to a height

of 15 meters or more. The fruit reminds one of a dried-up coconut. The oil from *C. brasiliensis* was analysed in 1868 by Peckolt (79) and later by Machado. The results published were entirely misleading, as shown by Dias da Silva in 1926 (23). The latter finds that the oil closely resembles chaulmoogra oil, the fatty acids consisting chiefly of chaulmoogric and hydnocarpic acids in about the same proportion as in chaulmoogra oil, with a small admixture of saturated acids. Peckolt's carpotrocholeic acid was not found in the oil. The findings of Dias da Silva have been confirmed by Jamieson (44) and by Rothe and Surerns (100). The macerate of the green fruit and the aqueous decoction of the bark of the twigs are used in Brazil as insecticidal washes for cattle. The pulp of the green fruit is employed as an expectorant, and the ground seeds or the seed oil is applied externally for skin affections. The oil and esters are being used at present in South America and the Carribean area in the treatment of leprosy (2, 23, 44, 49, 62, 79, 100).

There also occur in Brazil *C. longifolia*, *C. integrifolia*, *C. amazonica* and *C. grandiflora* (49).

Oncoba brachiantera and *O. spinosa* are found in the Sudan. The latter has been analysed and found to contain neither chaulmoogric, hydnocarpic nor any other optically active fatty acid (49, 74).

O. echinata occurs in Sierra Leone, Guinea, and along the Ivory Coast. The plant is a shrub, growing in moist surroundings in primitive forests to a height of 4 to 6 meters. The fruit contains many seeds, 2.5 centimeters in diameter, and is provided with spines like chestnut burrs. The seeds are called *gorli* or *katoupo*. The oil resembles that of *H. alcalae* in having a high melting point and in containing little or no hydnocarpic acid. The free fatty acids from the oil consist of 87.5 per cent chaulmoogric acid and 12.5 per cent of unsaturated liquid acids. It is also reported to contain a more highly unsaturated, optically active fatty acid similar to chaulmoogric but with one more double bond (*gorlic acid*) (3, 25, 29, 49, 63, 74).

O. glauca or *Caloncoba glauca* (*Oncoba klainii*) is found commonly in the French Cameroon. The seeds contain a cyanogenetic glucoside. The oil is similar to that of *O. echinata*. Peirier (80) finds that the specific rotatory power of the fresh oil is considerably higher (60.°8 determined in Cameroon) than that of old oil (40° determined in France) (63, 80, 88).

O. welwitschii is found in the French Cameroon. The physical constants of the oil from the seeds of this shrub are very similar to those of *O. echinata* (63, 80).

CHAULMOOGRA-GROUP OILS

Though, as is evident, oils containing chaulmoogric and, usually, hydnocarpic acids are obtainable from a considerable variety of plants, most of the oils now used in the treatment of leprosy are from *H. wightiana* and *H. anthelmintica*. The true chaulmoogra oil, from *T. kurzii*, has in recent years been used less and less for a variety of reasons; it is expensive, the supply is not dependable, it does not keep well, and it usually contains a high percentage of free fatty acid when it is placed on the market. There seems to be little difference in the efficacy of these three oils. Their chemical compositions, as far as shown, show a close similarity, and in general, they contain approximately the same amount of hydnocarpic and chaulmoogric acids, which are believed to be the therapeutic agents in the oils.

That *H. wightiana* and *H. anthelmintica* oils are used clinically in preference to other oils of this group does not necessarily mean that they are superior in their chemical or therapeutic qualities; it is rather due to the fact that they are obtainable readily in large quantities at the present time. There is reason to believe that adequate supplies of many of the other oils would be available were there a demand for them. In fact, plantations of the most desirable species could be set out easily were it known which is the most desirable. An accurate qualitative and quantitative analysis of all the oils of this group would appear to be a fundamental necessity.

NATURAL PRODUCTS OTHER THAN CHAULMOOGRA

Dilo oil, a product obtained from *Calophyllum bigator*, a plant native to the Fiji Islands, was used by Neff (72) on leprosy patients. He found that while it was not as effective as *H. wightiana* oil it did have an alleviating effect on nerve pains when given intramuscularly. Glasgow (28) has very recently analysed this oil. It consists of 9.7 per cent resin acids and 90.3 per cent fatty acids. The latter are palmitic (14.1 per cent), stearic (11.0 per cent), erucic (3.0 per cent) oleic (48.0 per cent), and linoleic (14.3 per cent). About 0.25 per cent unsaponifiable matter identified as sitosterol is present in the oil.

Cod liver oil as well as its ethyl esters and sodium salts (sodium morrhuate) has been used in the past by several workers in leprosy with some reported good effects. The oil is often given nowadays as an adjuvant in the treatment of leprosy. The composition of the oil is very complex. It contains the glyceryl esters of the common fatty acids, palmitic, stearic and oleic, together with a number of characteristic fish-oil acids (clupanodonic and others) which have not been so fully investigated. These fish-oil fatty acids are all unsaturated. De Vera has shown that in a series of oils of diminishing unsaturation (cod liver, soy bean, olive, coconut), the greater the unsaturation the greater the therapeutic value, corroborating Rogers and Muir's results (20, 95, 98, 99, 108).

Eucalyptus oil has been used to some extent. Hollman reported that it is of value in reducing nerve pains.

Gurjun oil (from *D. laevis*, *D. tuberatus*, *D. trinervus*) was found entirely useless by Hansen (30). Later trials in India had the same negative results.

Gynocardia odorata was long considered to be the source of chaulmoogra oil. The seeds are entirely different from those of *T. kurzii*; the oil contains neither chaulmoogric nor hydrocarpic acids and is not optically active. Although these facts were published by Power in 1905, the chemical terms gynocardic acid and gynocardate were used for many years when referring to the chaulmoogra-group fatty acids. It is only within the past six years that they have given place to the correct nomenclature.

Margosa oil (neem oil), known in India as "*melia azy radachta*", was reported on favorably in the treatment of leprosy when first used. It contains a characteristic unsaturated fatty acid belonging to the linolic series. It does not contain either chaulmoogric or hydrocarpic acid (11, 73).

Pangium edule oil, once thought to contain chaulmoogra-series acids, has been found by later workers to be optically inactive (85).

Hoang-nan bark from *Strychnos gaultheria* was used by various workers during the nineteenth century in Tonkin, Trinidad, Hawaii, and elsewhere. Early observations were encouraging but were not followed by continued improvement. The early beneficial effects were probably due to the fact that the essential principles in this drug are strychnine and brucine (30, 49).

TABLE 2.—Characteristics of *chaulmoogra*-group oils
I. *Hydnocarpus* oils

Species ^a	Per cent oil in seeds	Specific gravity	Refractive Index	Freezing point or melting point	Specific rotatory power	Iodine number	Saponification value	Acid value	Free fatty acids	
									Freezing point or melting point	Specific rotatory power
<i>H. alkalae</i> (8)	40.	0.950 at 30°	1.477	32° m.p.	+49.6	93.1	189.	3.9	59° m.p.	+53.6
<i>H. alpina</i> (42)	62.7 ^b	---	---	---	+47.6	---	---	---	39.2° f. p.	+50.1
<i>H. antheilmindica</i> (89)	16.3	0.953 at 25°	---	24° m.p.	+52.5	86.4	212.	7.5	42° m.p.	+53.6
<i>H. antheilmindica</i> (60)	---	0.946 at 20°	1.474	21.8° m.p.	+49.3	94.1	209.	0.6	---	---
<i>H. antheilmindica</i> (85)	12.2	0.952 at 30°	1.468	16° f. p.	+46.4	84.5	201.	3.6	36° m.p.	+50.
<i>H. cauliflora</i> (87)	---	0.946 at 30°	1.473	25° f. p.	+42.0	84.	201.	0.8	42° m.p.	+38.
<i>H. dawsonis</i> (77)	35.	0.853 at 35°	1.476	---	+38.8	91.4	182.	---	---	---
<i>H. heterophylla</i> (50)	32.	0.952 at 27°	1.468	---	+43.1	73.3	194.	0.9	---	---
<i>H. hutchinsonii</i> (85)	---	0.943 at 30°	1.474	23° f. p.	+46.6	83.5	199.	5.3	93° m.p.	+50.
<i>H. ilicifolia</i> (60)	36.1	0.947 at 20°	1.476	25.6° m.p.	+51.2	89.7	213.	0.6	---	---
<i>H. octandra</i> (42)	66.7 ^b	---	---	---	+54.1	---	---	---	48° f. p.	+54.
<i>H. subfalcata</i> (85)	35.9	0.951 at 30°	1.476	21° f. p.	+51.5	89.	206.	6.6	41° f. p.	+36.
<i>H. venenata</i> (7,42)	51.1 ^b	0.947 at 30°	1.477	19° m.p.	+52.	99.1	200.	4.4	43° m.p.	+60.9
<i>H. verrucosa</i> (77)	10.9	0.852 at 35°	1.475	---	+43.6	81.1	202.	---	---	---
<i>H. wightiana</i> (85)	41.2	0.947 at 30°	1.476	11° f. p.	+54.0	97.0	207.	6.7	40° f. p.	+54.
<i>H. wightiana</i> (89)	41.2	0.958 at 25°	---	22° m.p.	+57.7	101.3	207.	3.8	41° m.p.	+60.4
<i>H. woodii</i> (43)	61. b	0.899 at 100°	1.471	28.5° m.p.	+53.1	85.8	202.	32.8	44° f. p.	+54.4

II. *Asteriastigma*, *Tarakogenos*, *Carpotroche* and *Oncoba* oils

<i>A. macrocarpa</i> (87)	---	0.936 at 30°	1.471	---	+36.	87.5	201.	8.2	50° f. p.	+89.
<i>A. macrocarpa</i> (77)	47.	0.950 at 35°	1.479	---	+52.8	112.3	196.	---	---	---
<i>T. kurzii</i> (90)	30.9	0.951 at 25°	1.476	22° m.p.	+52.	103.	213.	23.9	44° m.p.	+52.6
<i>T. kurzii</i> (85)	28.8	0.951 at 30°	1.477	9° f. p.	+46.	104.	215.	3.4	32° f. p.	+43.0
<i>C. brasiliensis</i> (23)	---	0.95 at 25°	1.474	16° f. p.	+54.	108.	185.	2.6	---	---
<i>C. brasiliensis</i> (44)	66.	---	1.479	---	+58.9	113.	201.	0.1	---	---
<i>O. echinata</i> (3)	45.	0.929 at 32°	1.474	41° m.p.	+56.2	98.	185.	---	---	---
<i>O. echinata c</i> (25)	48.	0.944 at 12°	1.473	44° m.p.	+50.	95.	190.	0.0	56° m.p.	+50.3
<i>O. glauca</i> (80)	40.2	0.928 at 45°	1.468	39° m.p.	+40.	84.3	187.	3.0	---	+47.5
<i>O. welwitschii</i> (80)	35.6	0.939 at 45°	1.472	40° m.p.	+47.7	99.	194.	5.8	---	+50.

^a Numbers in parentheses refer to references at the end of this review.^c Seeds from cultivated plants.^b Per cent oil in kernel without shell.

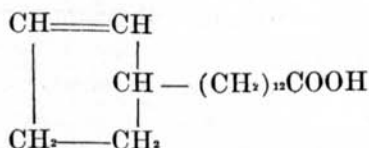
PROPERTIES OF CHAULMOOGRA-GROUP OILS
PHYSICAL CHARACTERISTICS

As has been shown, the group of chaulmoogra-group oils is a fairly large one. However, because until very recently interest was confined to only a few, most of these oils have been only superficially examined. Their analysis is not without difficulty, for it has not been possible up to the present to separate quantitatively the hydno-carpic acid from the chaulmoogric, or these from other fatty acids.

Nevertheless, the literature contains a considerable amount of data on the physical characteristics of these oils. These are collected in Table 2, the first section of which deals with the *Hydnocarpus* oils, the others being collected in the second section.

CHEMICAL PROPERTIES

The outstanding feature of this group of oils is their content of the unsaturated, optically active chaulmoogric and hydno-carpic acids. These peculiar fatty acids are characterized chemically by the presence in the molecule of a closed ring of five carbon atoms, whereas the ordinary fatty acids have all their carbon atoms in open chain structure. The empirical formula of chaulmoogric acid is $C_{15}H_{22}O_2$; the generally accepted structural formula is:



This structure was proposed by Power as one of two tautomeric forms. Shriner and Adams (¹⁰⁷), and later Perkins (⁸⁴), confirmed the above form but consider the other at least doubtful. Hydno-carpic acid is a homolog of chaulmoogric acid differing only in containing two less (CH_2) groups, the empirical formula being $C_{13}H_{18}O_2$. These acids contain an asymmetric carbon atom and turn the plane of polarized light strongly to the right. As chaulmoogric and hydno-carpic acids are almost unique among fatty acids in this respect, this property is a very valuable one in determining their presence or absence in an oil.

These two acids contain a double bond in the pentene ring and are therefore theoretically classed as unsaturated fatty acids; they absorb iodine and bromine in theoretical amounts. Unlike other unsaturated acids, however, they are solid instead of liquid, having

fairly high melting points; being solid acids, they behave more like saturated acids as regards their physical characteristics. The solubilities of their salts lie in general between those of the corresponding salts of the common saturated and those of the unsaturated fatty acids. On this account none of the ordinary schemes for the quantitative separation of saturated from unsaturated fatty acids can be used satisfactorily in their case. Qualitatively the two acids can be separated by fractional crystallization from alcohol, by fractional vacuum distillation of their ethyl esters, or by fractional precipitation of their barium salts.

Hydnocarpic and chaulmoogric acids are only sparingly soluble in the cold in the usual organic solvents with the exception of chloroform and ether, in which they are easily soluble. They crystallize from alcohol in lustrous plates. In this form hydnocarpic acid is readily attacked by the air but if allowed to solidify after melting it keeps fairly well. Chaulmoogric acid is more stable than hydnocarpic acid. The physical characteristics of these acids and their methyl and ethyl esters are given in Table 3.

Dean and Wrenshall (124) have found another optically active, highly unsaturated fatty acid in chaulmoogra oil. It is probably $C_{27}H_{42}COOH$, a chaulmoogric acid with another double bond, since it yields dihydrochaulmoogric acid upon catalytic hydrogenation. André and Jouatte (3) have isolated a similar acid ($C_{28}H_{44}O_2$) from the oil of gorli (*O. echinata*) which they have named gorlic acid. They have not obtained it in the pure state. They suggest that the extra double bond may be in the side chain. Power, et al. (89, 90) and Cole (13) have found evidence of the presence of a lower homolog of hydnocarpic acid in chaulmoogra and wightiana oils.

ACTIVE INGREDIENTS AND MODE OF ACTION

For years many workers believed that the reputed therapeutic quality of the chaulmoogra group oils was due to a glucoside or some other substance present in only small amounts. This idea was partially dispelled after Walker and Sweeney (119) demonstrated in vitro that the bactericidally active substances of chaulmoogra oil are the fatty acids of the chaulmoogric series. They decided that the bactericidal action of these fatty acids must be specific, for other unsaturated acids like those contained in linseed and cod liver oils have only a slight effect, which they ascribe to a non-specific soap action. Furthermore, although hydnocarpic and chaulmoogric acids are

TABLE 3.—*Characteristics of optically active fatty acids and esters*

Compound	Specific gravity	Melting point	Boiling point	Specific rotatory power	Iodine value	Remarks
Hydrocarpic acid (89) (a)	59°	+68.1	100.2	Lustrous leaflets
Hydrocarpic acid (87)	60°	+70.7
Methyl hydrocarpate (89)	8°	200-203° at 19 mm	+62.4	Colorless oil
Ethyl hydrocarpate (89)	211° at 19 mm.	+51.6	Colorless oil
Chaulmoogric acid (4, 90)	68.5°	247° at 20 mm.	+62.1	90.1	Lustrous leaflets
Methyl chaulmoograte (90)	0.9119 at 25°	22°	227° at 20 mm.	+50.0	Colorless oil
Ethyl chaulmoograte (90)	0.9074 at 15°	230° at 20 mm.	+50.7	Colorless oil

(a) Numbers in parentheses refer to references at the end of this review.

strongly bactericidal against acid-fast organisms, they are practically inert against non-acid fast organisms. Their conclusions were that the specific action must be associated with the cyclic arrangement of the molecule in these two acids and not with simple unsaturation. Lindenburg and Pestana (57) also believe that they act as direct chemotherapeutic agents, rather than as stimulants for phagocytosis or as tonics, but they come to the conclusion that the action can be mainly but not entirely ascribed to the unsaturation of the fatty acids.

Schöbl (105) concluded from in vitro experiments that the growth-inhibiting power of chaulmoogra oil depends on the structure of the ring of the fatty acids; when the structure of the ring is changed by saturation with hydrogen, the oil loses this biologic property. On the other hand, Hasseltine (33) using dihydrochaulmoogric (saturated) esters in vivo reported results almost as favorable as with the ordinary mixed esters.

Lie (56) believes that the action of the oil can be attributed to a solvent effect on the fat-containing cell of the bacillus, thereby liberating the endotoxin and thus inciting to action the antitoxic reaction processes in the body. Mackenzie (59) also explains its action on the lipolytic theory. Rogers and Muir (66, 99) suggest that the chaulmoogra oil stimulates the formation of lipase and that the increase of lipase increases lipolysis, thereby dissolving the waxy coating of the organism; the bacilli become free, form antigens, which results in frequent repeated weak reactions which finally lead to cures. They state that although the chaulmoogra-group oils may possess other principles which make them active, their usefulness is due probably in large part to the presence of the closed carbon ring as well as to unsaturation, while the effect of linseed and other oils with high iodine value is due to unsaturation. They also believe that a considerable part of the benefit derived from injections of these oils or their compounds is due to the local reaction produced by injecting an irritating substance into the tissues. On the other hand, Lara and Lagrosa (53) have very recently demonstrated, by using esters of different degrees of irritation (ethyl stearate and oleate), that local inflammatory processes produced by injections of the iodized esters of *H. wightiana* oil are not a necessary or even an important factor in the improvement observed. Muir (70), more recently, has come to the same conclusion by intradermal use on the same individual of alepol and hydnocarpus ethyl esters of the same degree of irritation; the latter showed much more favorable results.

Wayson (120) believes that the chaulmoogra-group oils and their derivatives have no specific therapeutic value and any effect that they may have remains undetermined.

Adams and others (109) have made and tested a great many new synthetic compounds in vitro on leprosy bacillus cultures. They find that solubility and bactericidal action reach the highest point when the molecule contains 17 to 18 carbon atoms. The kind, or even the presence, of a ring in the molecule is of lesser importance. The position of the carboxyl group in the molecule is of importance because it affects the solubility and surface tension. The bactericidal effect increases as the carboxyl group approaches the center of the carbon chain. The presence of a double bond is not important. A clinical test of one of these compounds (ethyl-di-normal heptyl acetate) by Lara (52) on 50 patients indicated that it was not quite as effective as the wightiana ethyl esters. Since this synthetic compound was very irritating, a further trial of the glyceryl ester (corresponding to a natural oil) was made. This ester acted like paraffin in the tissues; it was non-irritating but was not absorbed and was found to be useless.¹

Hollman and Dean (40) were the first to test the action of pure ethyl chaulmoograte in vivo. However, their patients were given chaulmoogra oil at the same time, so that their results could not be attributed solely to the pure ester. McDonald and Dean (58) subsequently treated ten unselected cases, five with ethyl chaulmoograte and five with ethyl hydnocarpate and showed that these compounds could arrest the course of the disease and cause evidences of the disease to disappear. They expressed the opinion that hydnocarpic was more active than chaulmoogric acid, and suggested that isomers of lower molecular weight might prove still more active. Hasseltine (33) claimed better results with the mixed esters than with the single esters, presumably from later data based on the ten patients of McDonald and Dean. Lara, et al. (21) furnished more extensive data on the efficacy of these compounds by treating for one year three selected comparable groups of twenty-five patients each, one group on chemically pure ethyl chaulmoograte, one on chemically pure ethyl hydnocarpate and one on the mixed ethyl esters of *H. wightiana* oil. All three compounds were iodized with 0.5 per cent iodine to reduce irritation. The ethyl chaulmoograte and ethyl hydnocarpate were found equally but only slightly superior to the mixed esters in

¹ Private communication from Dr. C. B. Lara.

obtaining clinical improvement. This superiority he believes, is due to their freedom from inactive constituents. In the light of more recent experiments by him, which will be described later, on the effect of iodine in olive ethyl esters and wightiana ethyl esters (54), it is unfortunate that it was found necessary to iodize these esters.

THERAPEUTIC PREPARATIONS OF NATURAL PRODUCTS

USE OF THE WHOLE SEEDS

For many years attention of persons treating leprosy has been directed almost exclusively to the oils and their derivatives. However, some use has been made of preparations containing chaulmoogra seeds.

Travers, in the Federated Malay States, used a mixture which he called "Tai-fong-chee" after its principal ingredient, kernels of chaulmoogra seeds. To two parts of these were added one part each of seeds of *toh mah jan* (*Canibis indica*) and *pak chut lai*, all ground to a sort of meal. He reported improvement in 82 per cent of 127 cases over a two-year period (49, 113).

In China and Indo-China various formulas are used which contain chaulmoogra seeds, and mixtures have been described that contained 20 or more ingredients. Such a preparation, containing a large proportion of charcoal, has been used for years by a native practitioner in a Government-supported leper village in Cambodia.

USE OF THE CRUDE OIL

Until comparatively recently there was a strong belief that the crude oil contained some element not in refined oil that made it more effective, and in fact this idea has not been entirely abandoned. In all probability this idea was largely responsible for the fact that until 1908 no attempt was made to utilize a purified chaulmoogra-group oil or a derivative thereof; nothing but the crude oils or seeds were used.

The oils as obtained on the market were often not pure, containing more or less solid, insoluble material, and were often rancid, with a high content of free fatty acid. These oils were given chiefly by mouth (41, 91, 114); to a small extent they were used by local application, but only seldom by injection. The objection to their use by mouth was that they had a nauseating effect on the patient, and only the strongest could retain doses large enough to obtain favorable results from the treatment. When so given the average tolerated dose ranged from 3 to 10 grams daily. The injection of the crude oil was very painful, and often caused abscesses.

These conditions ultimately led to efforts to obtain less irritating products that could be used by injection. Two lines of approach were followed, one designed to arrive at chemical modifications of the oil, the other to devise mixtures of the crude oil with bland or anti-irritant substances.

Engel, in Germany and Egypt, followed the first line and prepared the ethyl esters of chaulmoogra oil for injection. This product, which in patented form was put on the market as early as 1908, and others (notably Rogers' sodium salts), will be discussed later in this article.

Mixed preparations containing the crude oil, such as one containing liquid paraffin, had little success until Mercado, in Manila, under the stimulus of Heiser, prepared the mixture known by his name. This, which consisted of chaulmoogra oil, camphorated oil, resorein and ether, could be borne on injection better than the oil alone, and usually good results from its use were reported in 1913 and subsequently (34, 65).

USE OF REFINED OILS

In recent years attention has been directed toward the production and use of refined oils. This has been more for treatment by injection than by mouth, for at least there seems to be no definite relation between the degree of tolerance and the purity of the oil when given by mouth. The fatty acids themselves are better tolerated by mouth than the oils, up to 24 grams daily.

When used by injection, however, it is a well established fact that old oils are very much more irritating than oil from fresh, selected seeds, cold pressed. On the other hand, a purified oil is less irritating when used intramuscularly, subcutaneously or intradermally than even the best quality crude oil.

Perkins (87) has published a method of refining the oil which yields a very satisfactory product. The oil is washed with a solution of caustic alkali, the soap removed by repeated washing with hot water, and after separation of the oil, the volatile impurities are removed by blowing steam through the oil for an hour. If the oil is properly refined it yields a bland, non-irritating product to which it is not necessary to add any analgesic substance. The purified oil should not have a free fatty acid content of over 0.3 per cent.

Vahram and others have used a very fine, very dilute emulsion of chaulmoogra oil with gum acacia and water, which is marketed

under the name "collobiasis of chaulmoogra". It was used in the Philippines in 1920-21 with no promising results (102, 111).

Rogers and Muir (99) recommend the use of a good grade of crude wightiana oil with 4 per cent creosote for treatment by injection. They believe that creosote adds to the therapeutic effect.

Chaulmoogra-group oils to which 0.5 per cent iodine is added become so viscous that difficulty is experienced in attempting to use them by injection. Valenti (116) has prepared an iodized chaulmoogra oil, of butter consistency, containing 8 per cent iodine.

Johansen (45) used 10 parts of a 30 per cent solution of benzocain in olive oil to 90 parts of unrefined chaulmoogra oil to reduce pain on injection. For internal use of the oil, addition of strychnine, benzocain, and rhubarb have been recommended (49).

Supposedly pure, whole chaulmoogra-group oils, clear when melted and without excessive acidity, sometimes mixed with some other, bland oil but usually not, and without addition of any anesthetic or other irritation-reducing substance, are used extensively for injection in some regions, especially in Japan. In some instances weekly injections of comparatively very large doses are given. Were such oils on the market twenty years or so ago the development of chaulmoogra derivatives might well have been delayed.

DERIVATIVES OF NATURAL PRODUCTS

The very large doses that were required to obtain any apparent results when treatment was by crude oil given by mouth, besides the fact that many could not tolerate this form of treatment at all, directed attention insistently on the possibilities of treatment by injection. For this purpose an improved, less irritating preparation or form of the drug than the Mercado mixture was required. For a considerable period of years interest has very largely been in chemical derivatives.

Aroused by the work of Rogers in India (1915), and workers in Hawaii shortly after, there was a marked increase in treatment activity. With this there have been further advances in the preparation and administration of the chaulmoogra-group derivatives.

SODIUM SALTS OF CHAULMOOGRA-GROUP OILS

Such a compound was made for Rogers, in India, who in 1915 reported on its use under the name of sodium gynocardate (97, 101). This was a water-soluble preparation of the mixed fatty acids, and

was used, at first, in 1 to 3 per cent concentrations, subcutaneously and intramuscularly, later intravenously.

These salts may be prepared by saponification of the oil by various methods (21, 81, 82). Muir (67) advocates the use of the low melting fraction of the sodium soaps obtained by fractional crystallization. He states that this fraction when used intravenously blocks the veins less than that of the salts from the whole oil. This is also claimed for the proprietary preparation "Alepol".

There is some difference of opinion as to the relative efficacy of the sodium salts and the oil or iodized ethyl esters. The salts have not been found nearly as satisfactory as the esters by Culsion workers, while on the other hand, they have been used fairly extensively by workers in India, Africa and China. In such places as Africa and China where cost and difficulties of transport enter in, the sodium salts in the dry state have a decided advantage, and their popularity may be due to this fact. Recent comparative tests (68) seem to indicate that the iodized esters are decidedly superior for intradermal use.

Boez, et al. (5) prefer to give the salts by mouth as keratin-coated pills. Lampe (51) and others recommend the use of the sodium salts as soaps or ointments.

Sodium hydnocarpate, pure, was tried as a 1 per cent, almost neutral solution on 5 cases at Culsion in 1927. At the end of the trial not a single case had improved. The sclerosing effect in the veins was much less marked than with the original sodium gynocardate of Rogers and slightly less than with 1 per cent alepol. Buffered solutions of sodium hydnocarpate were also used on a few cases.

Sodium chaulmoograte, pure, is too insoluble for use by injection.

ETHYL ESTERS OF CHAULMOOGRA-GROUP OILS

The ethyl esters of these oils were originally prepared in the pure state by Power, in 1905, and were first manufactured for sale, with the composition not stated, under the trade name "antileprol" by Bayer and Company, in 1908. However, little attention was paid this form of the drug until 1918, when Dean and Wrenshall (18) prepared the mixed acids and ethyl esters of chaulmoogra oil in sufficient quantity for clinical trial. Their purpose was to obtain a derivative that would be less viscous, more readily absorbed and therapeutically more effective than the oil itself. Hollman and Dean (40) in 1919, reporting good results in the treatment of a large group

of cases, were instrumental in stimulating interest in this drug. The workers at the Culion colony, in the Philippines, made advances in its preparation and administration, and much experimentation has been carried on elsewhere. The mixed ethyl esters were originally prepared by first liberating the free fatty acids from the oil (the Bayer patent on antileprol), but the process was later shortened considerably by simply treating the oil directly with alcohol and a small amount of acid as catalyst. The simplest method is that suggested by Rogers and Muir (89), which involves the interaction of the oil and ethyl alcohol in the presence of sunlight (or heat) and subsequent washing with sodium hydroxide and water. In order to obtain comparatively nonirritating esters by this process, the original oil must be nonirritating. Cole recommends the distillation of the ethyl esters in order to get rid of extraneous substances, excess oil, etc. The esters must then be carefully neutralized and blown out with steam in order to eliminate irritating substances. Esters made by this process are more limpid, more constant in composition and less irritating.

Ethyl chaulmoograte and ethyl hydnocarpate.—The ethyl esters of the purified fatty acids of chaulmoogra-group oils have been used on a few cases in Hawaii and Culion, as described elsewhere. These compounds are nearly colorless liquids with a slight ethereal odor. Their physical characteristics are given in Table 3. They were first prepared by Power and his co-workers in 1904. Ethyl chaulmoograte is most easily obtained by preparing the ethyl esters from oil which contains the glyceryl chaulmoograte but not the hydnocarpate, such as *A. macrocarpa*, *H. alcalae*, or *O. echinata* oil. It may then be separated from other esters by fractional vacuum distillation. When hydnocarpic esters are also present the most careful fractional vacuum distillation is not sufficient to separate the two esters. Since none of the oils yet analysed contain only hydnocarpic acid, the isolation of this acid (or ester) is more difficult. Fractional distillation of the esters, must be followed by liberation of the acids in the fractions rich in ethyl hydnocarpate. These acids can then be fractionally crystallized in 80 per cent alcohol until pure hydnocarpic acid (melting point 60°) is obtained. Ethyl hydnocarpate may then be prepared from the pure acid (4, 87, 89, 90).

Iodized ethyl esters.—The ethyl esters alone have an inherent irritant quality which obviously cannot be removed since it is due to the configuration of the molecule. However, iodine in 0.5 per

cent concentration reduces the irritant effects very greatly, if it is added in a proper manner. The conditions of temperature and time of heating must be controlled carefully, according to Cole (14, 15). He has shown that sunlight or heat in the presence of air soon changes iodized esters in such a way as to make them extremely irritating. Iodized esters prepared in the above fashion do not show the separation of a black gummy mass, mentioned by Dean, even after several years standing.

Iodine was originally added, first in 4 per cent concentration, because it was expected to have therapeutic value. However, it was later concluded that it had no effect other than that of reducing the irritating properties of the ethyl esters (33, 104, 118), and for this effect it has been used by a few workers ever since. This viewpoint has very recently been brought into question by Lara (51). He has shown that iodized olive ethyl esters *when given intradermally* compare favorably with iodized wightiana ethyl esters, while plain olive ethyl esters are far inferior. This would indicate that, after all, the iodine does play a role in the therapeutic effect of the drug. It is interesting to note that the total amount of iodine per patient over a six months' test in this experiment was between 0.5 and 1 gram. Lara¹ has also recently shown on a very large group of patients that wightiana ethyl esters with 1 per cent iodine give better results (over a 6 months period) than the drug with 0.5 per cent, and that the drug with 2 per cent iodine gives still better results. The drugs were iodized by the standard method of Cole and showed no increase in irritant property with the increase in iodine content (up to 2 per cent). The results of this and the preceding experiment would seem to bring up once more the question of the value of iodine in the treatment of leprosy. It may be that the esters are acting as a store house for iodine, liberating it constantly but in such small amounts that strong lepra reaction is not induced as is often the case when iodides are used alone.

Creosoted ethyl esters.—Creosote was used as early as 1838 by Hjort, and later by Danielssen, without any good effect. Samson and Limkako (103), investigating the value of Muir's "E. C. C. O." mixture, found creosote of some value as an adjuvant. Wade (118) reported that chaulmoogra ethyl esters with 10 per cent creosote reduces the local irritation to almost, though not quite, the same degree

¹ Private communication.

as does 0.5 per cent iodine and permits increased medication, the only drawback being that there is an apparently greater tendency to cause respiratory-tract irritation. Muir, Cochrane and others have recommended the use of wightiana ethyl esters with 4 per cent creosote, or a mixture of equal parts oil and ethyl esters with 4 per cent creosote.

Other combinations with ethyl esters.—Other substances besides iodine and creosote have been added to the ethyl esters or the oil or to mixtures of both to increase their therapeutic effect or to reduce their irritant properties, acting in the latter case as diluents or analgesics. Such substances are olive oil, camphor, guaiacol, thymol, phenol, and anesthetin. While reported on favorably in the past they have, with the exception of olive oil, been largely superseded by the iodized esters. As an antiseptic, iodine has been found superior to other substances added.

OTHER ALKYL ESTERS

In Hawaii and at Cullion several of the other alkyl esters (propyl, butyl and amyl) were prepared and given trials (33, 83). Although giving results possibly comparable with the ethyl esters, no advantage has been found in the use of these to justify the greater cost of manufacture. Many other esters of hydnocarpic and chaulmoogric acids have been made by West and his co-workers but have not been tried out clinically (36, 121).

OTHER DERIVATIVES FROM CHAULMOOGRA-GROUP OILS

Wrenshall has prepared other salts of chaulmoogric acid which are soluble in water. One of these, the chaulmoogryl derivative of p-phenetidine sulphonic acid has been given a 6 months' clinical trial with unsatisfactory results. He has recently prepared another compound which may prove more promising, as the free acid compound is soluble in oil and the sodium salt is soluble up to at least 20 per cent in water. This compound is chaulmoogryl ortho amino benzoic acid.¹ He had prepared earlier two mercury derivatives of chaulmoogric acid and iododihydrochaulmoogric acid (19).

Power and Gornall (90) prepared chaulmoogryl alcohol, chaulmoogryl chaulmoograte, chaulmoogramide, di-hydrochaulmoogric acid, brom di-hydrochaulmoogric acid, and methyl di-hydrochaulmoograte. Dewar (22) obtained a high yield of chaulmoogryl alcohol by using the method of Prins. She also prepared chaulmoogryl amino benzene arsonic acid. Derivatives of chaulmoogric acid prepared by

¹ Private communication from Prof. R. Wrenshall.

West have already been mentioned. Naegeli and Stefanovitsch (71) have prepared several new derivatives of chaulmoogric acid.

Hinegardner and Johnson (37) have prepared resorcinol compounds of chaulmoogric acid and tested them in vitro and on rats. Cole (16) has prepared the lead, barium and magnesium salts of hydnoearpic and chaulmoogric acids and determined their solubilities as the first step in devising a method for the separation of these two acids.

Seabra (106) recommends copper carpotrochate, the "crystallized copper salt of carpotrochic acid in iso-tonic colloidal solution". He was probably using copper chaulmoograte or hydnoearpate or a mixture of both. (See *C. brasiliensis*).

INORGANIC SALTS

Antimony preparations.—Cawston (10) used colloidal antimony in sodium chloride solution on a few cases of leprosy and reported good results. He believed that the drug dissolves the fatty capsule of the organism; he stated that sulphur should be given at the same time to avoid the danger of metal poisoning. Hasseltine (33) and other workers did not obtain such good results, although a beneficial effect on leprosy ulcers sometimes was seen. Rodriguez and Eubanas (96) found potassium antimony tartrate (tartar emetic) more harmful than helpful. On the other hand, Muir finds it of value in lepra fever, and Hoffman (38) finds antimony compounds helpful as adjuvants. Other compounds, such as stibenyl, antimosan, stibosan, oscol, and red antimony sulphide have been tried by various workers with contradictory results.

Arsenical preparations.—Arsenic was considered harmful by Danielssen. Hallopeau and Aine reported temporary improvement by the use of atoxyl. Most workers have found salvarsan and epar-seno useless in leprosy. Other arsenicals which have been tried without favorable results are neosalvarsan, novarsenbenzol, silver salvarsan, copper salvarsan, hectin, arrhenal and cacodyl (49, 99).

Copper preparations.—Cyanocuprol ($\text{CuCN}\cdot 2\text{KCN}$) was found by Sugai (112) and other Japanese workers to have an apparently beneficial effect in a few cases of leprosy. Matta and Devoto (64) could not confirm these results, but claimed beneficial results with cupro-iodase, a "lipoid of copper, iodine and cholesterol". Henderson and Chatterji (35) find copper chloride-para diazo-amino benzene hydrochloride of some use in producing reactions but it has no

direct effect on the organism. Other copper salts that have been tried include copper sulphate, citrate, acetate, and hyposulphite (49).

Gold preparations.—According to Feldt, gold is not parasitocidal, but acts by increasing the body defenses through the means of the reticulo-endothelial system. There seems to be the same diversity of opinion as to the efficacy of gold salts in leprosy as exists in regard to antimony. Some workers claim good results, others none or harmful results. Lopion, krysolgan (4 amino-2 auro-mercaptobenzol + sodium carbonate), triphal (auro-thiobenzimidazol-sodium carbonate), auro-potassium cyanide, sanocrysin (sodium auric thio-sulphate), solganol (di-sodium salt of 4 sulphomethyl-amino-2 auro-mercaptobenzol 1-sulphonic acid), solfocrisol and orotiol (sodium aurosulphide) have been used (49). Paldrock (75) and Hoffman (39) claim good results with lopion, krysolgan and solganol, while Eubanas (24), Paneth (76) and Muir (69) find most of these salts of little or no use.

Iodine and Iodides.—Iodine, chiefly as iodides, has been employed for many years in the treatment of leprosy. A good summary of its therapeutic use in leprosy previous to 1911 is given by Currie et al. (17). These preparations have long been known to cause both general and local reactions when administered to leprosy patients. It has been suggested that this is in some way connected with the stimulation of cellular activity, bringing about an absorption of bacillary products. Marchoux and Bourret (61) noted that the iodide reaction in cases of leprosy is always accompanied by the destruction of a large number of lepra bacilli, which under the action of the drug lose their acid fastness. Currie et al. used, besides potassium iodide, iodoform emulsion in olive oil and inhalation of ethyl iodide. The latter invariably produced febrile reactions. Muir claims potassium iodide is useful but he admits it must be used with extreme care in order to avoid severe reaction. He suggests that the use of iodides be determined and controlled by the application of the red-blood-cell sedimentation test. Most workers feel that iodine in any of its present forms (except iodized oils or esters) is too dangerous for routine use.

Mention has already been made of Lara's unpublished recent experiments with iodized olive oil and wightiana esters iodized with 0.5, 1 and 2 per cent iodine. In view of these results, it seems likely that the use of iodine in leprosy therapeutics will be extended in the future if methods of controlling the reaction involved are developed

either by the use of new combinations of iodine, or by new methods of administration of the drugs, or both.

Other compounds of iodine which have been used are: airol (bismuth subgallic oxyiodate), aristol (di-iodo-di-thymol), europen (isobutyl ortho cresol iodide), iodoginoilo (ethyl cinnamyl benzoyl allyl ester of the fatty acids of chaulmoogra oil with 2 per cent iodine), sodium iodide, iodide of iron (49, 99).

Mercurial preparations.—The application of mercurials to leprosy is very old, dating from the thirteenth century (Gilbertus Anglicus, Paracelsus, Bernard Gorlonus). Pjetursson in Iceland, in a book published in 1769, claimed good results. Crocker recommended the use of mercuric chloride in 1896. Hansen, using various mercurials, found them valueless. Calomel, mercury cyanide, benzoate, bi-iodide, bi-iodate, mercurochrome, and 2-miristoxo mercuri-3-hydroxy benzaldehyde have been used. Temporary benefit has been observed but no lasting beneficial effects have been obtained in a large number of cases so far by the use of mercurials (49, 99).

Other inorganic compounds.—Such compounds as calcium chloride, calcium potassium manganate, collargol (silver salt), bixmixel (iodobismuth-quinine), basic bismuth salicyl, bismuth salicylate, sodium bismuth tartrate, lead sodium tartrate, platinum sodium chloride, sulphur, sulphates of the rare earths, colloidal tellurium, tellurium bi-iodide and radium have been tried on a few cases of leprosy with no outstanding results (32, 49, 104, 110). Sodium bicarbonate has been used to reduce nerve pains in leprosy (102).

ORGANIC COMPOUNDS

Quite a number of organic compounds have been tested, either alone or in conjunction with other drugs. Among these are cantharidin (sodium salt), chinosol, cholesterine, creosote, fuchsine, guaiacol, ichthyol, methylene blue, methyl violet, petroleum, phenacetine, phenol, quinine, resorcin, sodium cinnamate, strychnine, tannin, thymol, urotropin and xylol (49). With the possible exception of creosote, thymol and guaiacol, they have shown no promising results. Ephedrine has been recommended for nerve pains by Muir and by Cochrane (12). Eucalyptus and dilo oils, as well as sodium bicarbonate, have already been mentioned as being of possible value in this respect. Tetradotoxin has been recommended by Japanese workers for this purpose. Adrenaline, antipyrine, benzocain, cocain, and calcium chloride have also been used. Lara finds iodized wight-

iana ethyl esters injected around the nerve superior to other drugs for this purpose.

SYNTHETIC PRODUCTS

Chaulmoogric acid was first synthesized from simple organic compounds by Perkins (86) in 1927. It was found to be inactive (dl form) but was identical with the natural dextro-rotatory substance in other respects. Perkins also synthesized other compounds similar to chaulmoogric acid and one of these (sodium cyclopentene acetate) was tested clinically but gave only temporary beneficial results. Adams (1) later made the dextro rotatory chaulmoogric acid by starting with the natural hydnocarpic acid. He has made a large number of synthetic compounds, some of them similar to chaulmoogric acid. They have been tested for their bactericidal properties in vitro, as mentioned earlier in this review. There is no likelihood of synthetic hydnocarpic or chaulmoogric acids replacing the natural compounds now in use, as the method of synthesizing is a tedious and costly one. Other synthetic compounds of simpler structure might be prepared cheaply enough if, in the future, any are found to be superior to our present drugs in chemi-motherapeutic value. Synthetic compounds made by Dewar (22), Dean, Wrenshall and Fujimoto (19) and Hinegardner and Johnson (37) have already been mentioned.

PATENTS

The following patents have recently been issued for drugs with possible therapeutic value in leprosy:

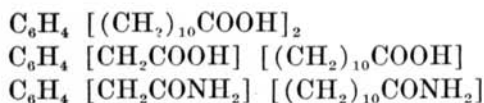
Cyclopentenylalkylacetic acid.—Roger Adams (to Abbott Laboratories), U. S. 1,677, 123, July 17, 1928. [From Chemical Abstracts, **22** (1928) 3266.]

Cyclopentenyl-substituted aliphatic acids.—Roger Adams, Carl R. Noller and James A. Arvin (to Abbott Laboratories), U. S. 1,678,175, July 24, 1928. [From Chemical Abstracts, **22** (1928) 3491.]

Aralkyl esters of hydnocarpus oils.—Examples, benzyl, phenethyl, para methoxyphenethyl, etc. esters. I. G. Farbenind. A-G. British patent 311,236, May 7, 1928. [From Chemical Abstracts, **24** (1930) 920.]

Diethyl-aminoethanol esters of hydnocarpus oils.—F. Hoffman-La Roche & Co., A-G. Swiss patent 139,326, Nov. 27, 1928. [From Chemical Abstracts, **25** (1931) 775.]

High molecular dibasic acids.—Example, benzene di-hydnocarpic acid:



Pierre M. Baranger, French patent 679,041, Nov. 27, 1928.

[From Chemical Abstracts, **25** (1931) 970.]

Aralkyl esters of hydnocarpus oils.—Example, phenyl ethyl ester). Ludvig Taub (inventor) to I-G Farbenind. A-G. German patent 529,811, May 8, 1928. [From Chemical Abstracts, **25** (1931) 970.]

Quinine salt of gynocardic acid.—Chemische u. Pharmazentische Fabrik. Georg Henning. German patent 527,712, Nov. 23, 1929. [From Chemical Abstracts, **25** (1931) 5284.]

Bactericides for acid-fast bacteria.—Roger Adams (to Abbott Laboratories, Inc.) U. S. 1,873,732, Aug. 23, 1932. Substances such as ethyl diheptylacetate or other aliphatic acids or their alkali or alkaline earth metal salts or hydrocarbon esters in which the carboxyl group is located at a point other than at the end of the chain and in which 10-21 carbon atoms are present. The acids of this character may be used in treatment of leprosy. [From Chemical Abstracts, **26** (1932) 6072.]

PHARMACOPOEIAL DESCRIPTIONS OF CHAULMOOGRA OIL¹

UNITED STATES PHARMACOPOEIA, 1926.

Oleum Chaulmoograe; Chaulmoogra Oil; Ol. Chaulmoog.

The fixed oil expressed from the seeds of *Taraktogenos Kurzii* King (Fam. *Flacourtiaceae*). The fixed oil from the seeds of certain species of *Hydnocarpus*, when designated as such and when agreeing in physical and chemical characters with Chaulmoogra Oil, may be used in its place.

Description and any physical properties.—A yellow or brownish-yellow liquid, or, at temperatures below about 25°C., a whitish, soft solid. It has a characteristic odor, and a somewhat acrid taste.

Chaulmoogra Oil is sparingly soluble in alcohol; soluble in benzene, chloroform, ether, and in petroleum benzin.

Tests for identity.—Specific gravity: about 0.950 at 25°C. The specific rotation $[\alpha]_D$ of Chaulmoogra Oil determined at 25°C. in chloroform, containing about 10 gm. of the oil in each 100 cc. of the solution, and using a 100 mm. tube, is not less than + 48° and not more than + 60°.

¹ Efforts to secure in Manila the official British, German and French descriptions were unsuccessful.

Tests for purity.—Dissolve 1 gm. of the oil in 15 cc. of a mixture of equal volumes of alcohol and ether, previously neutralized with tenth-normal sodium hydroxide, using 5 drops of phenolphthalein T. S. as indicator, and titrate the solution with tenth-normal sodium hydroxide to the production of a pink color which persists for fifteen seconds: not less than 1.8 cc. and not more than 5 cc. of tenth-normal sodium hydroxide is required (free acid).

Saponification value: not less than 196 and not more than 213.

Iodine value: not less than 98 and not more than 104.

Preserve in well-closed containers, in a cool place, protected from light.

Average dose, metric, 1 cc.; apothecaries, 15 minims.

JAPANESE PHARMACOPOEIA, 4TH EDITION.

Oleum Hydnocarpae; Hydnocarpus Oil.

A fixed oil obtained by expression from the peeled seeds of Hydnocarpus.

A whitish or yellowish, ointment-like mass, having a faint characteristic odor and a characteristic, fat-like, not acrid taste.

At 22-23°, the oil almost completely liquefies, and at 25-30° it melts completely to a clear liquid. Iodine value: 80-90. Saponification value: 195-215. Degrees of acidity: not less than 7.

Dissolve 5 gm. of the oil in pure chloroform to make it measure 100 cc. at ordinary temperature; optical rotation $[\alpha]_D$ at 20° of the solution is about + 24°.

Add 1 drop of sulphuric acid to 5 cc. of a chloroform solution (1:10) of the oil, and shake; a beautiful green color is produced after a short time.

Add 5 drops of a mixture of 1 gm. of trichloroacetic acid and 4 drops of hydrochloric acid to 10 drops of the oil, and warm gently; a deep blue color should be produced.

Warm the oil with 5 times its volume of absolute alcohol; a clear solution should be obtained, which deposits a white, crystalline precipitate at ordinary temperature.

SPANISH PHARMACOPOEIA, 8TH EDITION, 1930.

Oleum Chaulmoogra; Oil of Chaulmoogra; Oil of Ginocardia.

A fatty product obtained by pressing the seeds of *T. kurzii*, King, from Malasia and India, and from other species of *Hydnocarpus*.

Solid greasy mass of variable consistency, of whitish-yellow, dirty-yellow, or greenish-yellow color of characteristic heavy odor and having a somewhat acid or burning taste. It is slightly soluble in alcohol, soluble in ether, chloroform, carbon bisulphide, benzene and fixed oils.

Density at 15° = 0.93. Melts at 26° to 30° and solidifies at 20°. Dextrorotatory $[\alpha]_D = 52^\circ$ to 60° . Iodine No. = 95 to 106. Saponification No. = 196 to 213.

Mix 10 cc. of alcohol with 10 cc. of ether, add 5 drops of phenolphthalein (SR), and add drop by drop N/10 solution of NaOH until a red color persists for seconds. Then add one gm. of chaulmoogra oil and with a graduated burette add N/10 NaOH solution until the pink color persists for the same time as before.

From 2 to 5 cc. should be necessary (*maximum free acidity*). Preserve in well stoppered bottles.

Dose at one time — 1 gm.; Dose in 24 hours — 5 gm.

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