

trated has a caustic action on the skin and mucous membrane. It is free from odor, except when heated or mixed with an alkali, when the fishy smell is evolved. The taste of a solution of this salt is alkaline, but not disagreeable (Dujardin-Beaumetz). Dose, grs. ij to grs. v every three hours.

**ANTAGONISTS AND INCOMPATIBLES.**—Chemically trimethylamine is incompatible with the mineral acids, the salts of the metals, the alkalies (chlorides), and vegetable infusions. It should always be prescribed alone, in solution in some aromatic water. Therapeutically, it is antagonized by the stimulants, opium, belladonna, digitalis, etc.

**SYNERGISTS.**—All agents depressing the vascular system and the temperature are synergistic.

**PHYSIOLOGICAL ACTIONS.**—Applied to the skin, mucous membrane, or areolar tissue, trimethylamine produces decided caustic effects, comparable to those which result from the action of ammonia. It excites gastric pain when taken into the stomach in considerable doses, and will, doubtless, cause a high degree of inflammation if incautiously administered. The most characteristic effects are the lowering of the action of the heart, the depression of the temperature, and the diminution in the amount of urea excreted. In the physiological state Dujardin-Beaumetz found, in some experiments on himself, that the chloride of trimethylamine lessened the temperature and the pulse, but these results were much more decided when it was administered in cases of acute rheumatism. The influence which this agent has on the excretion of urea is still more remarkable. The observations of Dujardin-Beaumetz show that a gradual but considerable decline in the excretion of urea is a constant result of its administration. On the other hand, Spencer says that the excretion of urea is sometimes increased, and, in one case in which the urinary discharge was carefully studied, the urine was almost trebled, and the urea more than doubled by the use of this remedy. If the diminution of the amount of urea were a constant result, as claimed by Dujardin-Beaumetz, the influence which trimethylamine has on the body temperature might be due to an interference with the combustion process. But the facts do not as yet justify the construction of a theory as to its mode of action.

**THERAPY.**—Thus far almost the only application made of trimethylamine is in the treatment of *acute rheumatism* and *gout*. In some cases it appears to produce almost complete relief after the administration of a few doses, but generally a longer time is required (Awenarius, Dujardin-Beaumetz, Spencer, Leo). It moderates, at once, the fever and the joint-pain, and very decidedly shortens the duration of the disease. It is said to diminish the tendency to cardiac complication.

This agent, having so decided an influence on the pulse, temperature, and excretion of urea, will in the future doubtless be applied to the treatment of other maladies.

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**Pilocarpus.**—Jaborandi. The leaflets of *Pilocarpus pennatifolius* Lemaire (Nat. Ord. *Rutaceæ*, *Xanthoxyleæ*). (U. S. P.)

**Infusum Pilocarpi.**—Infusion of pilocarpus ( $\frac{3}{4}$  ij—Oj). Dose,  $\frac{3}{4}$  ss —  $\frac{3}{4}$  ij. (Not official.)

**Extractum Pilocarpi Fluidum.**—Fluid extract of pilocarpus. Dose, 3 ss — 3 ij.

**Tinctura Pilocarpi.**—Tincture of pilocarpus ( $\frac{3}{4}$  iv—Oj). Dose, 3 ss — 3 ij. (Not official.)

**COMPOSITION.**—The important constituent is the alkaloid—*pilocarpine*—which possesses the physiological properties of the drug. It combines with acids to form salts. The salts of pilocarpine crystallize in the oblique system. In 1880 another alkaloid was discovered, and to this the name *jaborine* was given (Harnack und Meyer). Subsequent researches fully confirmed this (P. Castaing). These alkaloids are closely related in composition: probably identical, but having a different molecular arrangement. By heat, merely by concentration of an acid solution, pilocarpine is converted into jaborine (Hans Meyer); and by washing with absolute alcohol they are separated, when united, as is very often the case in the commercial article. As these two alkaloids differ very greatly in properties, it is not surprising that the observations made with pilocarpine at first were very discrepant. Chemically they differ in that the salts of jaborine do not crystallize, and they dissolve more easily in ether and less easily in water. Physiologically, they differ even more decidedly. Jaborine acts like atropine, to which pilocarpine is a physiological antagonist.

**Pilocarpinæ Hydrochloras.**—Hydrochlorate of pilocarpine. Minute, white crystals, deliquescent, odorless, having a faintly bitter taste and a neutral reaction. Very soluble in water and in alcohol, but almost insoluble in ether or chloroform. Dose, gr.  $\frac{1}{2}$ —gr. ss.

**ANTAGONISTS AND INCOMPATIBLES.**—The caustic alkalies, the persalts of iron, and the salts of the metals generally, are chemically incompatible. A remarkable antagonism has been shown to exist between pilocarpine and belladonna (Ringer and Gould).

**SYNERGISTS.**—Aconite, veratrum viride, gelsemium, and remedies



which paralyze the vaso-motor nervous system, promote the activity of jaborandi.

**PHYSIOLOGICAL ACTIONS.**—The taste of jaborandi is rather hot and pungent. The considerable doses of the crude drug required to produce physiological effects excite nausea and vomiting, especially if taken on an empty stomach. It has been shown, however, in recent experiments, that these results follow the use of the alkaloid; hence it may be concluded that not bulk alone is the cause of the gastric distress, but that it is one of the physiological properties of the drug.

The active principles of jaborandi diffuse readily into the blood. In about ten minutes after the infusion is swallowed, the face, ears, and neck become deeply flushed. Simultaneously perspiration begins on the skin, an abundant flow of saliva takes place, the nasal and bronchial mucus, and the tears, are increased, and watery diarrhœa may occur. It is said that, when the salivary secretion is greatly increased, that of the skin is relatively less so, and *vice versa* (Féréol), but this is not generally admitted. The quantity of perspiration poured out by the skin is enormous—the sweat runs from the body and soaks the clothes. The quantity of saliva discharged is also very great. Ringer reports that in two of his cases the amount of saliva was respectively twenty-two ounces and twenty-seven ounces. According to Petithau, the sialogogue effect is constant, the diaphoretic action is somewhat less certain, and the diuretic effect uncertain. These conclusions are in accord with the general experience.

The action of the heart is increased by jaborandi, but the arterial tension is notably diminished. The rise in the pulse-rate averages twenty beats, and the duration of this effect is about two and a half hours. A very distinct fall of temperature ( $0.5^{\circ}$  to  $2^{\circ}$  Fahr.) ensues when the sweating begins, and this decline of body-heat is maintained on an average about four and a half hours. According to Robin, Gillet de Grandmont, and others, a transient rise of temperature precedes the fall, but Ringer and Riegel deny the accuracy of this observation. In some subjects, very serious symptoms due to the sudden development of extensive pulmonary œdema have been observed by Thomas, Napier, Sanger, Jenkins, and others.

The nauseant effects of pilocarpus and its alkaloid are, it is probable, referable to the action which it exerts on the muscular layer of the stomach and intestines. Very active movements of these organs follow its administration, and even a tetanizing action is observed. Secretion of the mucous membrane is increased, due, doubtless, to stimulation of the pancreas and the glands of the mucous membrane (Harnack und Meyer, Morat).

The effects of jaborandi on children, according to Ringer, are, singularly enough, much less, for corresponding doses, than on adults,

as respects the flushing, the sweating, the salivation, and the temperature.

More or less drowsiness, both in children and adults, follows the profuse sweating, and pallor succeeds to the flushing. Chilliness is experienced with the cessation of the sweating stage. Languor and debility persist for some hours after the completion of the effects. The drowsiness is probably not due to a direct action of the remedy on the cerebrum, but to the greatly-diminished vascular tonus, and to the loss of fluid from the vessels. Vision is generally affected. The pupil is usually contracted, and the power of accommodation is impaired. No characteristic or constant changes in the fundus of the eye have been observed on ophthalmoscopic examination. Locally applied to the eye, jaborandi causes "contraction of the pupil, tension of the accommodative apparatus of the eye, with approximation to the nearest and farthest points of vision, and amblyopic impairment of vision from diminished sensibility of the retina." The eye resumes its normal state in about an hour and a half (Tweedy).

The results of experiment indicate that the action of jaborandi is paralyzant of the vaso-motor nervous system. The flushing of the skin is doubtless due to dilatation of the arterioles, and the increased action of the heart must be referred to the same cause. The sphygmograph demonstrates the lowering of the vascular tension. The decline in temperature must be referred chiefly to the profuse transpiration, but the depression of the vascular tonus may also somewhat influence this result. The data do not yet exist for a statement of the mode in which jaborandi excites the salivary and cutaneous secretions. It probably affects the end-organs of the excito-secretory nerves (Harnack und Meyer, Vulpian, Dujardin-Beaumez, Grocco, and others).

That pilocarpus stimulates the gravid uterus is affirmed by many observers. Vander Neg asserts that, when injected subcutaneously or into a vein, it promptly induces uterine contractions, or increases the energy of those already existing. Kleinwachter reports two cases in which it induced premature labor. Three injections of two centigrammes each produced this result in one case, and two injections sufficed in the other. Dr. Prochownick, of Hamburg, also reports two cases of eclampsia, in which the hypodermatic injection of hydrochlorate of pilocarpine inaugurated labor in a half-hour. It frequently fails, even in considerable doses, to have this effect. Of nine reported instances in which it was used to induce premature labor, in six it was successful and in three it had no effect. The cases in which uterine action has been induced were chiefly eclampsia, and hence there is an important source of fallacy.

Elimination of the active constituents of jaborandi probably takes place through the organs whose functions are so powerfully excited. It is a remarkable circumstance that the amount of urea passing out



in the sweat caused by jaborandi is enormously increased over the normal, amounting to from fifteen to seventeen grains. The urine is not increased, as a rule, but Gubler apparently demonstrated that small doses frequently repeated had a distinct diuretic action. His theory is based on the notion that, being a universal gland-stimulant, if the skin is not directly stimulated and the fluids directed to it, the kidneys will be acted on. In some instances the growth of hair has been promoted by the subcutaneous and topical application of pilocarpus (Prentiss, André, and others).

The experiments which have demonstrated the existence of a physiological antagonism between jaborandi and belladonna have thrown much light on the action of the former. When the heart of a frog is arrested in the diastole by jaborandi, it immediately recommences its beat when atropine is subcutaneously injected (Langley). When the superior ganglion of the cervical sympathetic, and the lingual, and the pneumogastric nerve are divided, jaborandi administered causes profuse salivary secretion; but this action is at once antagonized and the secretion arrested by the injection of atropine. These agents, therefore, are exactly opposed as respects their action on the nerve-endings in the salivary glands (Carville). The effects of one grain of atropine, in a boy poisoned by it, were, as respects the state of the mouth and skin, antagonized by thirty grains of jaborandi. In three men the perspiration and salivation caused by sixty grains of jaborandi were arrested by the subcutaneous injection of  $\frac{1}{160}$  of a grain of atropine (Ringer and Gould).

*Comparative Action of Pilocarpine and Jaborine.*—The differences in physiological action between these alkaloids are infinitely greater than the chemical. There does not exist a finer illustration of the importance of molecular arrangement to physiological action. Given two alkaloids having the same ultimate constituents, their actions become antagonistic by reason of an unknown molecular arrangement. Jaborine, in its effects on the heart, lungs, pupils, and salivary glands, is identical with atropine. In the whole range of physiological antagonisms, there is none more complete than that existing between atropine and pilocarpine. As in some specimens of pilocarpine—owing, doubtless, to faulty pharmaceutical processes—there is more or less jaborine, it is no longer difficult to explain how some observers have differed in their observations. As the effect of pilocarpine on the circulation and the sweat-glands is so completely antagonized by jaborine, it is in a high degree important, in prescribing the former, to secure a specimen free from the latter.

*THERAPY.*—Pilocarpus, acting as it does on the salivary glands, has been used with varying success in *mumps*, sometimes succeeding well, and then failing. According to Testa, if used in time it may arrest the development of the disease, and later may prevent metastasis.

In *salivation of pregnancy*, it has succeeded perfectly in a few instances, but fails often; atropine is generally much more certain and effective. It is contraindicated in all affections of the gastro-intestinal mucous membrane, and in weak heart due to disease of its muscular substance, or of its contained ganglia, or of the valves. It is a remedy of great value in *cardiac dropsy*, provided the contraindications above mentioned do not exist; its therapeutic power being much the same as the vapor, hot-air bath, and other means for promoting free diaphoresis. The effusions of recent *pleuritis*, *hydrothorax*, and *ascites*, have been quickly removed by this agent. In *asthma* with profuse expectoration (humid asthma), and in *bronchitis* with abundant, non-purulent exudation, it has often been very beneficial. It must be used with caution, or not at all, in the difficult breathing due to dilatation of the right cavities and great venous trunks. According to Berkhart, pilocarpine, injected subcutaneously, arrests the most violent paroxysms of *spasmodic asthma*, and the relief persists for some time. It is equally effective, in the author's experience, in *singultus* or hiccough, but there may be incurable lesions underlying the spasm, when, of course, the paroxysms may be expected to recur again.

Probably the most conspicuous good results from the administration of pilocarpine have been obtained in *eclampsia*, from the albuminuria of pregnancy, of scarlatina, or of acute Bright's disease. The powerful action on the sudoriparous glands, and the excretion of the urinary solids by the sweat, are the causes of the extraordinary relief obtained from this remedy in suitable cases. It should be borne in mind that pilocarpus tends to excite uterine action, and hence its administration may, under some circumstances, be improper; but in most cases this effect is desired. There are, however, two important contraindications: a weak heart, from thinning and atrophy of the walls of the organ, or from fatty degeneration, and a tendency to pulmonary congestion and œdema. In some instances, in a few minutes after the injection, the respiration became embarrassed by congestion and œdema of the lungs and by enormous bronchial secretion (Sanger, Napier, G. Thomas). It may be well to mention that atropine, subcutaneously, in one case in which it was administered, removed these symptoms and saved the patient's life. In *renal dropsy*, especially scarlatinal, there being no contraindication in the state of the heart, it is a remedy of the greatest utility.

Pilocarpine has proved to be an important addition to the resources of the ophthalmologist. In inflammatory affections with effusion and exudation it brings about resolution and absorption (Wecker). According to Coursserant, there is no remedy comparable to it in the *amblyopia of alcoholism and of tobacco-abuse*. It has produced excellent results in *detachment of the retina*, chronic *iritis*, *keratitis*,



hæmorrhages into the vitreous, floating bodies, glaucoma, *atrophic choroiditis*, hæmorrhages and exudations of the retina, commencing atrophy of the optic nerves, etc. (Gillet de Grandmont, Meyer, Gubler, Wecker, and others). The first-named author affirms that we find in pilocarpine "an absolute remedy against white atrophy." Beranger, following Gubler, proposes to use this remedy as a substitute for eserine in certain ocular affections requiring a myositic—an effect produced by pilocarpine when instilled in the eye. It has been used successfully *de novo* and as a substitute for eserine in certain paralyses of the ocular muscles—those consecutive to the fevers and other acute diseases. After the operation for cataract extraction, pilocarpine is used by Chalot to prevent exudations and other inflammatory changes. In the discussion which ensued before the Geneva Congress where this paper was read, various adverse opinions were expressed regarding the exhibition of this remedy in different ocular maladies. Especially was the danger emphasized—the danger in cases of cardiac and arterial diseases, and of pulmonary engorgement.

Ringer has used jaborandi with success to *increase the secretion of milk*. As the milk-glands correspond in structure to the sudoriparous glands, and are merely differentiated and specialized for their particular office, the effects of this drug in increasing the production of milk might have been, *a priori*, expected. The author has used recently a fluid extract of jaborandi successfully in a case of deficiency in the secretion of the milk of a nursing-woman. But Dr. Max Strumpf denies that it has such power.

In two cases of that very intractable disorder, *diabetes insipidus*, or polydipsia, Laycock has used jaborandi with the effect to reduce the quantity of urine in one case from three hundred ounces to one hundred and twenty ounces per diem, and, in the other, from one hundred and fifty-eight ounces to ninety-eight ounces per diem. M. Huchard reports the cure of a case of the same kind, and also one of *glycosuria*; on the other hand, Vulpian declares it to be useless. Murrell has found it to be useful in some cases of the sweats of phthisis and of other nocturnal sweats, but yet far inferior to atropine and picrotoxin.

In *scaly skin eruptions*, pilocarpus has good effects by maintaining a moist state of the skin. It is the most efficient remedy for *alopecia* which we possess. In the treatment of this affection pilocarpine may be injected subcutaneously, or the fluid extract can be applied locally. The following is a very successful topical application: ℞ Ext. pilocarpus fl., ℥ j; tinct. cantharidis, ℥ ss; lin. saponis, ℥ ijss. M. Sig.: The scalp must be well rubbed with this lotion daily. In *prurigo* Pick had success, but failed in psoriasis, and he also succeeded in two cases of *pruritus senilis* and in one of *urticaria*. In *alopecia pityrodes*, he had good results in ten cases, but not in *alopecia areata*.

Pick administered one sixth of a grain three times a day by the stomach.

Recently Guttman has brought forward pilocarpine as a remedy for *diphtheria*. He reports having successfully treated eighty-one cases without a single death, but these extraordinary results have not been confirmed. Numerous observations have been published, but out of the mass of cases and reports we can select only some of the most important. Soon after Guttman's paper appeared, confirmatory statements were published by Lax, and directly contradictory by Lashkevitz. The latter lost all his cases treated with pilocarpine. Pitschen and Dilewsky, on the other hand, succeeded in curing many which would otherwise, they think, have died. Archambault treated twenty-one cases according to Guttman's plan, and of these twelve died, a result which he considers bad. In this country Jacobi was one of the first to make a trial of the new remedy, and he pronounced against its utility. Payraudeau, who has made an exhaustive study of the subject, offers some conclusions which seem to the author eminently sound. The false membrane in inaccessible situations is softened and detached by the action of pilocarpine; it does not effect the elimination of the diphtheritic poison by the sweat which it induces; it is apt to cause nausea, vomiting, and diarrhœa, and may in this way greatly increase the danger of the case; it is positively contraindicated when the cardiac muscle is weakened in any way. Although these positions are perfectly tenable, there are facts more favorable to the utility of pilocarpine. They are well stated by Courtois: The results of the treatment of diphtheria by pilocarpine, without being so good as were at first supposed, are nevertheless worthy of careful consideration. Children of less than five years offer such slight resistance to the action of the morbid germs of diphtheria, that they are rarely cured. Those above this age, in which the mixed form of the disease is most frequent, are especially favorable subjects for this treatment. The false membrane is more thoroughly detached, and has less tendency to be reproduced, than by any other treatment. All are now agreed that efficient support must be given the patient by food and alcohol during the pilocarpine treatment; that cases characterized by extreme depression of the vital powers, and by weakness of the heart, are unsuited for this remedy.

Guttman exhibited pilocarpine with hydrochloric acid and pepsin by the stomach, giving from  $\frac{1}{8}$  gr. to  $\frac{1}{4}$  gr. Archambault administered the remedy by the stomach generally, but, in urgent cases, hypodermatically. Chiotti preferred rectal injections of a simple solution.

*Physostigma*.—Calabar bean. The seed of *Physostigma venenosum* Balfour (Nat. Ord. *Leguminosæ*, *Papilionaceæ*). (U. S. P.) *Fève de Calabar*, Fr.; *Kalabarbohne*, Ger.