AGENTS WHICH DEPRESS THE MOTOR FUNCTIONS OF THE SPINAL CORD AND SYMPATHETIC.

Conium.—Hemlock. The full-grown fruit of *Conium maculatum* Linné (Nat. Ord. *Umbelliferæ*), gathered while yet green. (U. S. P.) *Ciguë*, Fr. ; *Schierling*, Ger.

Abstractum Conii.—Abstract of conium. Dose, gr. ss—gr. ij.

Extractum Conii Alcoholicum. — Alcoholic extract of conium. Dose, gr. j—grs. v.

Extractum Conii Fluidum. — Fluid extract of conium. Dose, ♏ ij—♏ v—♏ xl.

Tinctura Conii.—Tincture of conium. Dose, ♏ x—ʒ j.

The preparations of conium are very uncertain in strength. It is pretty well established that the extracts are nearly, if not quite, inert. The best preparations are the fluid extract and alkaloid.

Composition.—The special powers of hemlock are due to a peculiar alkaloid (*conine*). This is an oily, limpid liquid, having a strong alkaline reaction, a peculiar odor resembling the urine of mice, and a specific gravity of 0·88. It probably exists in the plant in the form of the malate ; but, by some authorities, the acid with which it is combined is supposed to be an acid peculiar to conium, the *coneic acid.* Conine is associated with ammonia, and another crystallizable alkaloid, *conhydrine.*

Conine is quickly decomposed by heat. Exposed to the air, it is soon converted into a brownish resin, and becomes inert. Hence it is that the preparations of conium possess but little activity, and are so frequently, indeed entirely, wanting in physiological and therapeutical effects. It is better, therefore, to administer the alkaloid, which, being soluble in alcohol, may be administered in that menstruum, or it may be converted into an acetate and dissolved in a mixture of alcohol and water. It is to be noted, also, that different specimens of conine differ remarkably in activity ; hence, whenever a new preparation is begun, the minimum dose should be first administered until its real power is ascertained (Burman).

Conine.—Dose, gr. $\frac{1}{60}$—gr. $\frac{1}{20}$—gr. $\frac{1}{10}$, or in minim-doses from ♏ $\frac{1}{10}$—♏ ij. Half a minim of conine (pure) is about equivalent in activity to ℥ j of the best succus conii. The chlorhydrate and especially bromhydrate of conine are greatly to be preferred, not only to the pure alkaloid, but to any of the preparations of conium. The bromhydrate crystallizes in the form of colorless, prismatic needles, which are freely soluble in water and also in alcohol, have but little taste, and no odor (Mourrut). The dose of this salt ranges from $\frac{1}{12}$ of a grain to $\frac{1}{4}$, $\frac{1}{2}$, even 1 grain. It is not actively toxic. By reason of this fact, its freedom from a disagreeable taste or odor, and its solubility, the bromhydrate is a most desirable preparation for administration, either by the stomach or hypodermatically.

Antagonists and Incompatibles.—The caustic alkalies and tannic acid are chemically incompatible. Physiologically considered, the actions of conium are antagonized by nux-vomica and its alkaloids strychnine and brucine, by picrotoxin, and the tetanizing agents in general.

Synergists.—Gelsemium, tobacco, veratrum viride, aconite, methyl-strychnium, hydrocyanic acid, and curara, increase the action of conium.

Physiological Actions.—The preparations of conium possess a considerable degree of acridity, and are therefore apt to produce gastric irritation, nausea, and vomiting. These results sometimes follow the subcutaneous injection of conine. The active principles readily diffuse into the blood. What changes, if any, they induce in the blood are quite unknown. It is probable that they limit the power of the red blood-globules to convey oxygen to the tissues on which they have a selective action—the motor nerves.

When an active dose of conine is administered, weakness of the legs and a sense of weight and fatigue of these members are first experienced. The eyelids become heavy and droop somewhat, and double vision, or confused vision, a feeling of torpor of the mind, and giddiness, follow. Speech is also affected as respects vocal utterance, but the memory for words and the faculties of mind generally are unimpaired. When the dose is a lethal one, paralysis of the voluntary muscles—first of the inferior extremities—ensues ; there is considerable vertigo, the mind is torpid and indifferent but not perverted, speech and vision are lost, the respiration becomes labored and slow from paralysis of the respiratory muscles, and death occurs from asphyxia, the action of the heart continuing until after respiration has ceased. The mind remains unclouded to the last, except when delirium ensues from carbonic-acid poisoning. Convulsive movements generally occur in animals from retention of carbonic acid in the blood, and in man sometimes local convulsive movements. Sensation is unaffected until near the close, but a subjective sense of numbness is experienced in the feet and legs, without actual impairment of the functions of the sensory nerves. The body temperature is decidedly lowered, and in a direct ratio to the amount of the paralysis.

The physiological effects of conine, even when produced by decidedly large medicinal doses, are hindered if not entirely prevented by active exercise. When the muscular weakness, the heaviness and sense of fatigue in the legs are first experienced, if resisted and muscular movements are carried on, these sensations disappear, and the whole duration of the physiological effects is much shortened.

The action of conine is, primarily and chiefly, on the end-organs of the motor nerves ; the nerve-trunks next lose their excitability, and

by an extension of the paralysis the spinal cord is at last involved. The muscular irritability remains unaffected. According to M. Verigo, the paralysis proceeds from the spinal cord, outwardly, to the terminal filaments of the motor nerves. But it is probable that this experimenter operated with a preparation of conine containing methylconium, which has been shown, by Crum Brown and Fraser, to affect first the motor columns of the spinal cord.

No constant and characteristic *post-mortem* appearances seem to be produced by conine. The left cavities of the heart are found empty, and the right distended, but these are products of the mode of dying, and are not directly due to the action of the poison. The blood is generally fluid, and the coagula are soft.

Elimination takes place by various channels, chiefly by the kidneys. Conine has been found in considerable quantity in the liver, lungs, and spleen.

THERAPY.—Formerly the preparations of conium were much used for a supposed discutient or resolvent action in *glandular enlargements*, and in certain *kinds of tumors*. But, since it has been shown that the preparation chiefly employed for this purpose (the extract) is practically inert, the supposed cures effected in this way are justly regarded as examples of the *post hoc*. Influenced by the same considerations, conium was supposed to have an alterant and anodyne action in *cancer*. But, since, in the progress of physiological research, it has been shown that conium affects the motor and not the sensory nerves, it is no longer employed to relieve the pains, or to arrest the growth and diffusion, of cancer. It is right to add, however, that able practitioners hold that the discutient and resolvent powers of conium are well established in clinical experience (Stillé).

The true uses of conium are those deduced from a consideration of its physiological actions. As it lowers the functional activity of the motor nervous system, it is indicated in those cases of disease in which motor activity is in excess. Very valuable results have been obtained by the use of *conine* in *mania*, administered with the view of subduing excessive motor excitement. Its real utility consists in quieting muscular agitation, and thus preventing emaciation and maniacal exhaustion. It is considered to be most suitable to the treatment of *acute mania*, without organic brain-lesion (Burman). The dose required for this purpose is ♏ ss—♏ iij, or subcutaneously, commencing with one tenth of a minim, and gradually increasing it until some characteristic physiological effects are produced.

The succus conii has been used by Harley and others with success in *chorea*. The special object for which it is used in this malady is to quiet the excessive muscular agitation; but, in order to accomplish this result, a sufficient quantity must be administered to produce distinct physiological effects. To quiet muscular agitation is not alone sufficient to cure chorea; a suitable hygiene, proper alimentation, and restorative agents, are indispensable. Some cases of *paralysis agitans* are remarkably benefited by conium, but it is of little avail in cases of *sclerosis*, or when important structural alterations have occurred. Conine is certainly indicated in *tetanus*, *hydrophobia*, and *strychnine-poisoning*, but hitherto it has not succeeded, probably because inert preparations were employed. The author has ascertained that in animals conine rather hastens than retards the lethal effects of strychnine.

In *whooping-cough*, *asthma*, and *laryngismus stridulus*, good effects have been obtained by the use of conium, carried to the point of inducing its characteristic physiological effects. *A priori*, the best results might be expected from the use of conium in *epilepsy*, but it is by no means comparable to the bromides. According to Echeverria, conium is serviceable in those cases of epilepsy "attended by cerebral derangement and vertigo."

The state of *blepharospasm*, which accompanies *strumous ophthalmia*, is relieved by considerable doses of conium. It is necessary in the treatment of this, as of other motor disorders, to give a sufficient quantity of conium to produce sensible physiological effects.

The Hypodermatic Use of Conine.—The alkaloid itself is much too irritant for subcutaneous use. The local inflammation which it sets up prevents absorption, and hence the effects are *nil*. The alcoholic solution is almost equally objectionable. The following formula, proposed by Burman, is the best for the subcutaneous use of the alkaloid:

℞ Coninæ, ʒ iij, ♏ xij.
Acidi acetic. fort., ʒ iij, ♏ xij.
Spts. vini rect., ʒ j.
Aquæ destillatæ ad ℥ ij.

M. Sig.: *Dose, one minim to begin with, and gradually increase as necessary. Five minims of this solution contain one minim of conine.*

"The acid must be added carefully and gradually until neutralization, or as near an approach to it as possible, is attained; litmus-paper being used, from time to time, to determine the reaction." Different specimens of conine may require somewhat different proportions of acid to neutralize it. If the mixture be turbid after the addition of the spirit and water, a little more spirit may be added.

The subcutaneous injection of conine may be practiced instead of the stomach administration, in all of the forms of disease for which this remedy is prescribed. By Burman this mode of administration has been practiced with much success in the treatment of *acute mania;* by Pletzer, in *asthma;* by Erlenmeyer, in *emphysema* and *angina pectoris;* by Lorent, in *pneumonia* and *pleuritis;* and by Eulenburg, in *blepharospasm*. A marked decrease in the pulse-rate, and in the tem-

perature, has been observed to follow the hypodermatic injection of conine in these diseases. The rational indication for the use of conine in pneumonia and pleuritis is, to give the organs physiological rest by inducing a paretic state of the respiratory muscles.

A solution of bromhydrate of conine is greatly preferable to any form of the alkaloid, for all purposes, but especially for subcutaneous injection. The following will prove useful: ℞ Coninæ bromhydratis, gr. viij; aquæ, *vel* aquæ lauro-cerasæ, ℥ j. M. Sig.: Ten minims contain one sixth of a grain. As Tiryakian and also Tuloup have shown, the effect of this agent declines by repetition, and hence the dose must be increased every few days. Two doses every twenty-four hours will usually be sufficient to maintain a constant effect. By the authors above mentioned, by Dujardin-Beaumetz, Prevost, Rochefontaine, and others, it is asserted to be very effective in spasmodic affections, especially of the respiratory organs—in whooping-cough, asthma, dyspnœa, laryngismus stridulus, spasm of the glottis, hiccough, etc. It has been used with success in tetanus by Chisolm and by Cory.

Conine and Morphine.—The effects of conine are in every way heightened by morphine. These agents have been very successfully employed in acute mania, conjointly administered subcutaneously. "Conine acting on the purely motor centers, in a sedative manner, and morphine acting in a similar way on the sensori-motor and ideo-motor centers, it follows, as a fair corollary, that the combination of the two, in subcutaneous injection, should lead to effects directly antagonistic to the condition of maniacal excitement; and, such being in fact the case, they may be thus used together with very great success in the treatment of mania." When *nerve-pain* and *muscular spasm* coexist, the best results may be expected from the combined administration of morphine and conine.

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Curara, or Woorara.

History.—There are no official preparations. The substances known under this name vary much in purity, and differ in origin. True curara is a poisonous substance, prepared by the Indian tribes of certain districts of South America, and known under the names *woorara*, *urari*, *wurali*, etc. A specimen examined by Mitchell and Hammond consisted of two distinct preparations named respectively *carroval* and *vao*, the former more closely corresponding to the European specimens. Curara is obtained for the most part from several plants of the *Strychnos* family, as *Strychnos toxifera*, *S. cogens*, and from *Paulinia cururu.* An extract from these plants, it is supposed, is mixed with the venom of certain poisonous reptiles, and possibly with other animal substances. As the arrow-poison of different tribes differs not only in strength, but in the character of the effects produced by them, it is certain that they are derived from different sources. That which is now obtained in commerce as curara, and which agrees in the main with the description of Bernard, is the substance referred to in this article.

Composition.—Curara occurs in small, irregular masses, of a dark-brownish color, somewhat slimy, and looking like a dried vegetable extract. The mass is in part soluble in water, and the undissolved residue is composed, for the most part, of starch-granules, vegetable cells, oil-drops, and other vegetable structures (Mitchell and Hammond). The existence of an alkaloid in curara had been suspected by Boussingault, but it was not actually discovered until 1865, when it was isolated by Preyer. The estimates formed of its activity vary: by Preyer it was held to be twenty times stronger than the crude drug, but by Beigel only six times; but these differences are readily accounted for in the varying qualities and activity of curara.

Curarine, the alkaloid, is crystallizable, deliquescent, and forms with acids salts, which are also crystallizable. The dose will range from $\frac{1}{100}$ gr. to $\frac{1}{40}$ gr. by the stomach—from $\frac{1}{200}$ gr. to $\frac{1}{100}$ gr. when administered subcutaneously. A larger quantity may be necessary when distinct physiological effects are to be produced.

Mitchell and Hammond give the name *carrovalia* to the alkaloid which they obtained from carroval.

The dose of woorara or curara, the crude drug, will range from $\frac{1}{20}$ gr. to $\frac{1}{8}$ gr. It is desirable to try on some inferior animal the activity of any new specimen before using it on man.

Antagonists and Incompatibles.—As curara is a paralyzer, it is antagonized by those agents which act in the opposite manner on the spinal cord. From the physiological standpoint, strychnine and atropine are appropriate antagonists, opposing the tendency to death by failure of respiration. Remarkable results have been obtained in animals by artificial respiration. An animal will recover from twice the

fatal quantity, if respiration be kept up until elimination occurs, which is speedy. As in the case of the other alkaloids, curarine is destroyed by the caustic alkalies.

Synergists.—The paralyzers in general, especially the respiratory group, promote all of the actions of curara.

Physiological Actions.—The taste of curara is bitter. Applied to the unbroken integument, it is not absorbed ; but swallowed, it slowly diffuses into the blood, and produces characteristic effects. Vulpian finds that it is absorbed more rapidly when injected into muscular masses than when simply thrown under the skin. According to the observations of Voisin and Liouville, made on man, the salivary, nasal, and lachrymal secretions are increased. It is probable that the gastro-intestinal secretions are also promoted. The rate of diffusion into the veins from the stomach varies, but it takes place in from twenty minutes to a half-hour ; but even a longer time than this may be required. The action of the heart increases ; the pulse rises a number of beats and may be dicrotic ; the temperature ascends two to three and a half degrees, and the respirations are accelerated, four to eight times per minute being added to the usual rate. Voisin and Liouville ventured on the exhibition of larger doses with the following result : the symptoms began by a more or less violent chill ; the heart beat rapidly, reaching 140, and the pulse became weak ; the respiration was labored and sighing ; the temperature rose, and double vision, sometimes with mydriasis, sometimes with myosis, set in. The legs became weak, coordination was destroyed, and the vertical position could not be maintained. The mind continued undisturbed. The paralysis disappeared after a short time, but a sense of fatigue persisted in the limbs for some hours. The increased temperature was accompanied by the usual symptoms of fever—there were, besides the accelerated pulse and respiration, headache, thirst, and perspiration.

It was by means of curara that Bernard demonstrated the existence of contractility as an independent endowment of muscular tissue. Curara, by poisoning the end-organs of the nerves in the muscles, separated these organs, and thus permitted a study of the agency of each. In all classes of animals, as in man, curara induces paralysis of movements : locomotion, the erect posture, breathing, finally the heart's action, are arrested. The paralysis induced by curara is not due to an abolition of the excitability proper to the motor nerve-trunks, but to a modification set up in the terminals of the intra-muscular nerves. This fact is proved by the well-known experiment of Bernard, repeated by Kölliker, Zeleuski, Vulpian, and numerous other experimentalists, in which a frog is paralyzed by curara in all parts of the body except one limb which has been ligatured to prevent the access of the poison to it. The muscles of the unpoisoned limb react normally to stimulation, to the will, and to reflex impressions from distant parts. The

muscles of the poisoned parts of the body act on direct stimulation, but not by the will nor by any direct or reflex excitation conveyed by the nerve. The paralysis must therefore be due, as above stated, to the effect of the poison on the terminals of the nerve in the muscular tissue. As movements can be induced in the muscles of the unpoisoned limb by irritation of the skin at a distant point, it is clear that the sensory nerves and the reflex function of the spinal cord continue active. It has been abundantly demonstrated that in curarized animals the spinal cord preserves its functions for a long time. If, however, a large quantity of the poison is administered, and a fatal result prevented by artificial respiration, the excitability of the cord is at first increased but afterward paralyzed (Von Bezold, Vulpian, etc.). The motor and sensory nerve-trunks are also finally affected, but this is a secondary action, and ascertainable in curarized animals only by maintaining artificial respiration a sufficient length of time. It follows, then, that all parts of the nervous system are ultimately paralyzed. The action begins in the end-organs of the motor nerves, and then gradually extends to all parts, if the dose is large enough and life is maintained by artificial respiration.

Curara also acts on the accelerator nerves of the heart, at first stimulating and afterward paralyzing them. The action of the heart is increased, also, by the paralyzing effect of curara on the terminals of the pneumogastric, thus removing the inhibition. So decidedly is the vagus affected by full doses of curara, that galvanic irritation does not arrest the movements of the heart (Von Bezold). Notwithstanding the increased action of the heart, the blood-pressure is lowered by curara, due doubtless to a paralyzing action on the organic muscular fiber and consequent dilatation of the vessels. The effect of curara on the sympathetic is variously interpreted. According to Vulpian, the iris contracts on changes in the amount of light falling on the retina in curarized animals ; the pupils dilate on faradization of the skin ; dilatation of the vessels of the posterior members and an elevation of temperature take place in a curarized dog on faradizing the central portion of the corresponding sciatic ; very energetic reflex contractions of the stomach, intestines, and bladder are obtained in curarized animals by faradizing the skin of different regions of the body (Vulpian). These facts indicate that curara does not destroy but rather stimulates the functions of the sympathetic. Curara acts on the lymph-vessels of frogs. According to Tarchanoff, the liquid which accumulates during curarization grows richer in leucocytes ; also the blood contained in the vessels becomes more concentrated, the relative proportion of red globules being increased. As the accumulation of leucocytes takes place in the lymph-sacs, there is a corresponding diminution of them in the blood. These changes are due to the paralysis of the peripheric vessels (Tarchanoff).

Curara, as has been stated, produces an obvious rise of temperature in the extremities. This is supposed to be due to paralysis of the peripheral vessels. In the interior of the body, however, there ensues an equally constant decline of body-heat (Tscheschichin, Röhrig und Zuntz). This lowering of the central temperature is due to the loss of heat at the periphery by the cooling of the blood detained in the superficial vessels.

Bernard long ago ascertained that curarized animals became diabetic. It seems probable that this result is due to the paralysis of the vessels of the liver. On the other hand, Bock and Hoffmann have apparently demonstrated that the production of glycosuria is the result of increased activity of the liver. It may be due to the fact that the sugar formed does not undergo oxidation, for Jolyet has ascertained that in curarized animals the excretion of carbonic acid is much below the amount in health. By reason of the changes in the vascular supply, curara affects the functional activity of various organs. The increased production of saliva, and of the nasal and intestinal secretions noted at the outset, is due, there is little doubt, to this fact.

The elimination of curara takes place chiefly by the kidneys, but some escapes with the fæces (Koch). The urine of a curarized animal will poison another animal, and this may be repeated to several subjects. The retention of the urine charged with curara, in the bladder, will continue the effects of the poison by reabsorption. This statement has been the subject of considerable controversy. It has been denied that the mucous membrane of the bladder possesses the power to absorb again into the circulation poisons dissolved in the urine in the process of excretion. Brown-Séquard appears to have been the first to prove, by direct experiment, that alkaloids could be thus absorbed, and some recent observations have confirmed the accuracy of his experiments. In respect to curara, as to other organic alkaloids, when poisoning occurs, it is an obviously proper expedient to keep the bladder empty, if necessary, by catheterization.

Therapy.—The applications of curara to the treatment of disease follow from the results of the physiological study. Being a motor and not a sensory paralyzer, it is adapted to the treatment of *muscular cramp and spasm.* It is one of the remedies employed against *strychnine-poisoning,* and although from the theoretical standpoint such treatment may seem proper, yet in actual practice it has not succeeded. That a remedy obtained from members of the strychnos family, and a paralyzer in action, should antagonize strychnine, is a remarkable fact. In the process of preparation employed by the Indians, it is in a high degree probable that *methyl strychnium* is formed, and this substance, as was originally shown by Crum-Brown and Fraser, is a paralyzer, and acts precisely like curara. Curara has been used with a limited measure of success in *tetanus.* In the successful cases—for example, that narrated by Mr. Spencer Wells—large doses were administered. According to the statistics of Demme, of twenty-two cases of tetanus treated by this agent, eight recovered. Other methods have certainly succeeded better. Two cases of *hydrophobia* have been reported in which a cure followed the use of curara. One of these, reported by Dr. Watson, was examined, and the diagnosis confirmed by Dr. Flint, of New York. The first dose was $\frac{1}{16}$ gr., and subsequently $\frac{1}{9}$ gr. and $\frac{1}{6}$ gr. were given. The value of this statement is impaired by the fact that the different specimens vary so much in activity. M. Vella has successfully treated a case of tetanus by cutaneous absorption of the agent; but the usual mode of administration has consisted in the subcutaneous injection. This subject, as M. Vulpian has well said, has lost its interest since the discovery of the utility of chloral. It is in a high degree probable, however, that curara would be greatly more successful if it were pushed in these cases to obtain its full physiological influence, and the complete suspension of the spasms.

By Voisin and Liouville curara has been extensively employed as a remedy for *epilepsy.* The facts already mentioned in regard to the action of this agent in producing febrile phenomena were obtained from the experiences with epileptics. They find that attacks may be prevented, and the condition of epileptics much improved, by the timely administration of this remedy.

It has proved useful in *chorea,* in *tic-douloureux* (Beigel, Du Cazal), but other remedies are doubtless better.

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