Original Communications.

CONIUM MACULATUM.*

By LEONARD WHEELER, M.D., Lincoln, Ms.

THOUGH hemlock is immemorially familiar as a deadly poison to the people in every part of Europe, the advance in the scientific knowledge of its action has been far from keeping pace with that of other agents of apparently no greater value, certainly of no greater interest. For nearly a century it has been in the hands of physicians as a remedy, and largely used at different times in the treatment of various diseases. Notwithstanding this familiar use it has still received little attention from careful scientific men, especially chemists and physiologists.

Very little was really known as to the chemistry of conium previous to the discovery of its active principle forty years ago, and the knowledge of the physiological action is still in a very backward state. Reference to any modern book of therapeutics or *materia medica*, will show how unsatisfactory, apart from its toxic effects, is the knowledge in regard to it. Pereira acknowledges this ignorance, and Christison laments it as follows: "If physicians or physiologists would acquire definite information as to the physiological effects of hemlock, in small or medicinal doses, they must begin the inquiry anew. Little importance can be attached to anything already done in this field, as I have no doubt whatever that by far the greater proportion of the preparations hitherto employed, have been of very little energy, and in the doses commonly used, absolutely inert." In "*Headland on the Action of Medicines*" it is described as a general

sedative. Other books give no more valuable information.

On its action as a *poison*, many observations have been made and recorded—long ago, and more recently. Modern experiments on the *toxic* effects of conium on animals are so exhaustive and complete as to leave little to be added.

What is the cause of the uncertainty in regard to the medical use of this drug?

First, the plant is a difficult one to distinguish from others of the same class, and is influenced much in its quality by different conditions of soil, climate, and exposure—the juice of the plant grown in a dry place and sunny exposure during a warm season, being far richer in the active principle than that grown under the opposite circumstances of shade and moisture formerly recommended.

Moreover, it is an old idea, since discountenanced, but a second time pretty effectually proved, that the dried leaves lose, in the most careful drying, much, if not all, of the conia which they possessed when green. Geiger says, decisively, that the dried leaves contain no conia—Pereira, that no reliance can be placed on the dried leaves, however carefully prepared; for they sometimes yield no conia, though they possess the proper hemlock odor and a fine green color.

The importance of this point to our inquiry will be seen by reference to any *Pharmacopœia*. In that of the United States, we find four preparations of conium. Three of them are derived from the dried leaves.

This subject has been minutely investigated, and careful results obtained by several recent observers.

Dr. John Harley* subjected two carefully selected specimens of the dried leaves to the most approved methods for extraction of conia. In addition to this, he tried the effect on himself and various patients, even tottering convalescents, upon whom the physiological effect of the drug is most

* The old Vegetable Neurotics (Gulstonian Lectures, 1863).

* MR. EDITOR,—The following paper was presented to the Medical Faculty of Harvard College as the graduating thesis of its author. It contains a number of valuable and original observations with regard to an article of the *materia medica* whose physiological action has been little studied, and whose therapeutical value is not generally recognized. I advised Dr. Wheeler to send it to you for insertion in your JOURNAL, and commend it to your readers as worthy of their attention.

Very truly yours,
VOL. V.—No. 25

EDW. H. CLARKE.

easily produced, of doses from six to twenty-six times as large as those laid down in the Dispensatory, without producing any effect beyond that of the large amount of stimulus thus exhibited in the preparations made with alcohol.

From all his experiments, Dr. Harley came to the conclusion that the dried leaves contain little if any conia.

On the other hand, experiments show that in some cases preparations from the dried plant do contain a quantity of the alkaloid sufficient to render them useful.

Dr. Wm. Manlius Smith, of Manlius, N. Y.,* a careful and excellently qualified experimenter, tested the tinctures made from four specimens, gathered by himself, of the leaves and fruit, green and mature, fresh and dried. The tincture made from the parcels of leaves and seeds, after drying, yielded, much to his surprise, the same amount of active principle as the corresponding tinctures made from the undried specimens.

The conditions on which this variation depends, we do not know how to avoid. If, therefore, we would have any preparation free from all this doubt, these preparations from the dried plant must be discarded.

The extractum conii of the U. S. P. is made from the fresh plant; but in its preparation it is exposed to prolonged heat, which is at one stage raised to the boiling point. At this temperature the active principle is rapidly decomposed. Hence the comment of the Dispensatory, that no one of the extracts is more variable in its qualities than this.

There is no useful preparation of conium in our Pharmacopœia.

The English have a good preparation in the succus conii, which is merely the juice preserved in one third of alcohol. The variations in strength are not so great as to be a very serious objection, depending merely on the quality of the plants used in its manufacture.

The best American preparation of conium, so far as I have been able to discover, is Squibb's Fluid Extract of Conium Seed. It is remarked by all investigators of the subject, and noticed in the common books of materia medica, that the green fruit contains a much larger amount of the active principle than other parts of the plant, being from three to seven times as rich in conia. It suffers, also, little from drying or from keeping several years. The seeds should be collected before maturity—about the latter part of July.

* Am. Jour. Pharm., 1868, p. 459.

Squibb's preparation is made from such seeds, and is regulated in strength so that $\mathfrak{m}$ i. equals gr. i. of the same specimen of fruit dried; that is, the number of minims of fluid extract made from a quantity of powdered green seeds, is made to equal the number of grains which this quantity would weigh if dry. So that here, as with the succus of the British Pharmacopœia, the only chance of variability in strength, is in the quality of the vegetable itself, and by sufficient care in its selection this cause of deterioration is reduced to a minimum.*

This preparation I have taken in various doses a sufficient number of times to test its power in my own case.

In addition to this, we have the alkaloid conia. It is made by several manufacturers, but is quite rare here. I presume a standard quality is not obtainable.

The specimen which I have is made by Merck, of London. It is not a colorless liquid, as the pure alkaloid is described, but perfectly clear, and of a bright reddish brown color. It has a strong, impregnating, disagreeable odor, much like the urine of mice, is strongly alkaline, and exceedingly irritating. The taste is pungent and astringent.

Physiological Action.—The physiological action of conium is confined mainly, if not entirely, to the motor centres of the body.

On Animals.—I experimented with non-fatal doses of the alkaloid on the frog and rabbit. About $\mathfrak{m}$ $\frac{1}{2}$ was injected under the skin of the back of a medium sized frog, and the whole surface kept moist in order that the cutaneous respiration might be as perfect as possible. He was very active, as if in pain, for a few minutes. In eight minutes he began to be affected by the dose, drooping and keeping very quiet. In ten minutes he would lie on his back and allow his legs to remain in any position in which they were placed; lids drooping, respiration irregular and slow. At 14 minutes he was completely paralyzed, and, fearing that he was about to die, I exposed the heart, which was beating with fair strength, and continued as follows:

At 15 minutes,	pulse	48
" 20 "	"	"
" 35 "	"	44
" 40 "	"	40
" 50 "	"	39
" 72 "	"	27

During all this time the animal was to all appearance dead, except for a few slight convulsive jerks during the first few min-

* This extract is made by rep rectation, no heat being used in its manufacture.

utes, and for the action of the heart. Reflex action was not interfered with. Nothing could be determined as to sensation, the animal being unable to give evidence of pain. Having to leave the experiment after an hour and 12 minutes, I wrapped the frog in a wet cloth, and left it to die, as I supposed. On my return in three hours, he had escaped and was hopping about as well as ever. The effect of double this dose was much the same.

In two cases I watched the circulation in the web of the frog's foot with similar results, as follows: The dose—about $m\ ss$.—was injected, as in the previous case. First effect was in seven minutes, and in twenty minutes he was to all observation completely dead, except for the beating of the heart. The current in the capillaries of the web gradually slowed after a minute or two, and at seven minutes from the time the dose was taken, was stopped completely. It started again slowly in forty minutes, and from that time increased in rapidity till it became again normal. On the calibre of the vessels there was no effect. The pulse was as follows:

At 20 minutes	49	per minute
" 30 "	36	"
" 50 "	27	"
" 68 "	29	"

One very small drop ($m\ \frac{1}{2}$) was put into the eye of a rabbit. The poor creature screamed with pain and rubbed the eye; but was soon overwhelmed by rapidly increasing paralysis, commencing at the end of the second minute, and at twenty minutes so complete that the lids drooped so as nearly to close the eye; the limbs remained where they were placed, and the head fell to one side. Still, he was able, when urged, to draw himself feebly along. At eighty-five minutes he was able to raise himself on his hind legs, and was fast improving, particularly after his nose was thrust out of the window, though he seemed much inclined to sleep, or at least, to remain quiet with the eyes closed. He had apparently recovered in two hours. The pulse and respiration, so far as obtained, were as follows:

	Resp.	Pulse.
At 12 minutes	360	
" 20 "	232	
" 28 "	164	
" 45 "	140	260
" 75 "	140	300

(I was not able to get the healthy pulse and respiration, uninfluenced by struggling or fright.)

On Man.—I experienced the following

effects from a dose of Squibb's Fluid Extract of the Seeds. At 11.35 I took $3i$.; felt the first effect in about three-quarters of an hour, viz., a dull feeling of weight across the brows, so that I found myself continually pressing it with my hand—not painful at all, but feeling wrong; with it there was a very little vertigo on quick motion of the eyes or head. Soon after there was a general feeling of weariness, making me glad to lie down, which I did for a few minutes, feeling quite tranquil and comfortable as if resting after long muscular exertion, but not at all dreamy or sleepy. I got up and went to walk, feeling distinctly, as soon as I began to move, the oppressive dulness in the head and weakness of all the muscles; noticed in the arms when I put on my hat, and in the legs all the time; making a flight of stairs a most discouraging obstacle.

These effects were at their height in about three-quarters of an hour, continued for half an hour, and then began to decline. At two o'clock I ate dinner with an excellent appetite, and felt almost no effect afterwards.

From $m\ 30$ and downwards I felt no effect at all.

The effect from two drops of conia from the point of a fine pipette (about $\frac{1}{3}$ of a m) was much the same in character, though less in degree.

From double this dose ($m\ \frac{2}{3}$), the effect was greater than from $3i$. of the fluid extract. I took the dose at 12.10 o'clock. It produced a burning, astringent sensation in the throat, and afterwards a burning feeling (very slight) in the stomach. The conia was merely diluted with a large amount of water, or rather floated on its surface; if dissolved in alcohol and diluted there would probably be no difficulty in taking it.

As I sat reading, I felt the first effect in twenty minutes. In twenty-five minutes there was fast increasing heaviness of the eyelids. While the eyelids were shut, or while I kept steadily on reading, there was no giddiness or modification of intelligence. I could understand and weigh what I was reading as well as ever I could. But still it was only by considerable exertion that I could do this, because of the difficulty in keeping my eyes well opened and focused; the lids would fall together, and the lines seemed to get out of range, and I had again and again to devote my attention to fixing them—which I could do perfectly well when I tried. There was no inclination to sleep farther than that my muscles

felt weary, and my eyes were inclined to close.

In half an hour came the first feeling of muscular weakness, and desire for quiet, which was calm and delicious when indulged, like rest after a day's work. In forty-five minutes I started to walk, having the same dull oppression in the head, and feeling very weak. My gait was swaying and unsteady, and considerable determination was required to complete a half-mile walk without stopping to rest. On sitting down at the end of my journey, I dropped hard into the seat, though exercising the usual amount of caution. In an hour and a half the effect began to decline. At 2 o'clock I ate heartily and perceived no further action of the drug.

In all my experiments I have felt some coldness during the action of conium. In none have I noticed any effect on sensation, the pulse, or the intelligence. Neither have I perceived any hypnotic effect, except so far as muscular quietude, and the dropping together of one's eyelids tempt sleep.

The periods of absorption and elimination can be determined only by the presence of the symptoms of its action, which begin, when the drug is introduced in liquid form by the stomach, in half or three-quarters of an hour, and last from two to four hours. Conia cannot be discovered in any of the excretions.

The rapidity of the symptoms is astonishing. The patient is in a moment stricken with palsy, but in two or three hours there will remain no trace of this powerful influence.

The physiological action is then very limited, "and consists essentially of swift-spreading palsy of the muscles, affecting first those of voluntary motion, then the respiratory muscles of the chest and abdomen."* The primary seat of action is probably the spinal cord. Its effect is the counterpart of that of strychnia in that conium exhausts the nervous energy and leaves the muscles powerless, while strychnia irritates it, producing long and powerful contractions of the muscles. This, of course, suggests its employment in poisoning by strychnia, but there is no reason for hoping for any antidotal effect from it. It has been tried on animals poisoned with strychnia, with the effect of stopping the convulsions, but not much, if at all, delaying death. Its action in this case is perhaps similar to that of ether, which both

delays and alleviates the convulsions, but only slightly defers death.

The first symptoms that I have noticed, is the peculiar feeling of weight across the brows, soon associated with drooping of the lids, and difficulty in the adaptation of the eye; that is, partial paralysis of the third nerve. With larger doses other effects are noticed, from paralysis of other muscles supplied by this nerve, such as double vision and dilatation of the pupil. A little later weakness of the muscles of the legs is noticed, and in rapid succession all the voluntary muscles are involved.

Reflex action is not at all affected by medicinal doses and muscular contractility remains normal. Conium has no direct hypnotic effect, nor does it have any action in the sensory nerves. As to its effect on the sympathetic system, I am not satisfied. I have not been able to make out any effect on my own pulse, and Harley (op. cit.) says: "Except a transient emotional effect on nervous individuals, upon a sudden access of the symptoms after a first dose of hemlock, the heart and bloodvessels are absolutely unaffected by its operation." But there was certainly a marked effect on the pulse of the animals mentioned above, both in the frequency of the beat and the force, as shown by the stopping of the current in the capillaries of the frog's web, without any contraction of the vessels. That complete stasis should occur in both cases after the same interval, and be so prolonged without any contraction of the arteries, must be explained by the presence of some abnormal action.

The final action of conium is upon the involuntary muscles of respiration through which death results by asphyxia. Life is indefinitely prolonged if efficient respiration can by any means be kept up. Thus artificial respiration is the main resource in case of an overdose.

(For a corroboration of these views of its physiological action, and probably for much that is new on the subject, I must refer to a recent long essay on the "Experimental Study of the Physiological Effects of Conicine" (?) by M. Casaubon, a very short notice of which only I have been able to see.)

Dose.—The activity of Hemlock, as might be imagined from its physiological action, is not so much proportionate to the age or robustness of the individual, but depends more on the muscular activity, so that a slight restless child might be unaffected by a dose that would paralyze a strong man of sedentary or indolent habits.

* Christison Ed. Roy. Soc. Trans. vol. xlii.

And with the same individual at different times, a quantity which, after a long period of repose would be a full dose, might prove insignificant after a season of muscular activity. If a child while taking it recovers rapidly the ability to run about, a largely increasing dose will be found necessary.

The dose of the British succus is $\mathfrak{z}$ i. (sometimes less) to commence with, and goes up to $\mathfrak{z}$ vi. or $\mathfrak{z}$ i.

The dose of Squibb's Fluid Extract I can judge of through my own experience only. From $\mathfrak{z}$ ss. I got no effect; the result of a $\mathfrak{z}$ i. I have recorded. I undoubtedly require more than an average dose. For a child of two years, if moderately active, $\mathfrak{z}$ ss. might be a full dose. I should prefer to commence with $\mathfrak{m}$ x. or $\mathfrak{m}$ xv. and increase.

It is said that conia is unsuitable for internal use; but properly administered, I see no reason why it may not be employed. It is locally very irritating. The rabbit's eye into which I introduced it was very much inflamed, the lids were closed, and it discharged purulent matter for days; but at the end of a month I was unable to select that rabbit from his companions. As it is so irritating and is soluble only in alcohol and ether, we cannot use it hypodermically. But dissolved in alcohol and diluted with water, it can be taken by the stomach in commencing doses of $\mathfrak{m}$ $\frac{1}{2}$; or two drops may be dissolved in twenty-four drops of alcohol, and three drops of the solution given on sugar.

I have recorded the effect of $\mathfrak{m}$ $\mathfrak{z}$ on myself. There was a noticeable effect from half this quantity.

These three preparations—the British Succus, Squibb's Fluid Extract of the seed, (any other worthy manufacturer may of course be substituted), and the alkaloid Conia are the only ones fit for use.

Therapeutic Uses.—For small doses, that is, for doses short of those that produce some of the visible physiological effects, like tonic doses of quinine, we know of no use. *In order to apply hemlock to any remedial use, it is necessary to exhibit full doses, such as will produce unmistakably its paralytic effects.*

The study of the physiological action of conium discovers only one direction in which to employ the drug in the treatment of disease, namely, in convulsive muscular action resulting from irritation, direct or reflex, of the motor centres, in such diseases as the following. First and most important, convulsions or tendency to convulsions in

children, occurring so often at the time of dentition, chorea, convulsive action of particular muscle which sometimes occurs, paralysis agitans, epilepsy, tetanus.

"Hemlock is essentially a children's medicine. It has often appeared to me that in the early development of the body, motor activity, from a variety of exciting causes, is liable to a disproportionate development, and that thus a tendency to convulsive diseases often arises." (Harley, op. cit.)

As has been previously said, the modern experimental employment of hemlock has not yet been extensive and careful enough to establish and limit its field of usefulness; but still this can be accomplished with comparative ease when its theoretical use is attended with success. A careful study of physiological action may well take the place of statistics of empirical use. The not yet extensive use of conium, founded on the knowledge of its action, is, to a very encouraging degree, successful.

This general statement I shall allow to take the place of reports of cases which might be adduced in confirmation.

I have aimed in this paper, first, to show that all our officinal preparations of conium are, for various reasons, either totally inert, or so variable as to be practically useless.

Second, to indicate preparations of the drug suitable for use.

Third, to insist on efficient paralyzing doses, the amount of which will depend on the muscular activity of the individual.

Fourth, to explain the time, and mode of action.

Fifth, to indicate merely its therapeutic use.

DIFFERENTIAL INDICATIONS FOR THE USE OF LOCALIZED AND GENERAL ELECTRIZATION.

By A. D. ROCKWELL, M.D., and GEO. M. BEARD, M.D., of New York.

In order to determine the differential indications for the use of localized and general electrization, we need to consider these four facts:—

First, That general electrization *directly* affects the whole body, while localized *directly* affects only the part to which the application is made.

Secondly, That general electrization may, by sympathetic or reflex action, *indirectly* have a special therapeutic influence on some special part or organ, while localized electrization of any part, but especially of