

Francis M. Duncan

On.

The "Podophyllum Peltatum"  
with especial reference to the

Physiological & Therapeutic  
action of

"Podophyllin".

1.

The *Podophyllum Peltatum*, commonly known by the names of May-apple, Hog-apple or Mandrake, is an indigenous perennial plant, having its habitat in the shady woods of North America.

Concerning its early history little is known; it appears to have been used for a considerable number of years, prior to its introduction, as a recognised medicinal agent, by the native Indians of North America, from whom the first colonists of the country received a knowledge of its medicinal virtues, and by them again transmitted after a lapse of time to the regular medical practitioners.

When the first United States Pharmacopœia was issued in the year 1820, it received a place

in the primary list of the *Materia Medica*, a formula being likewise given for the preparation of an extract, and ever since it has appeared in each successive edition of the *United States Pharmacopœia*, and to show that it has not been lost in estimation I find it stated that about eighty thousand ounces of the resinoid principle *Podophyllin* were prepared in the *United States* during the year 1860.

It is only, as far as I can discover, within the last two years been introduced into this country.

Owing to the accounts given of it, by medical practitioners, regarding the action of its resinoid principle, and having seen it prescribed with beneficial results both in the *Royal Infirmary* and out-door Dispensary practice, led me to think it a suitable subject for Graduation Thesis; I accordingly obtained what parts of the plant could possibly be had, and the results of the observations I have made form the principal part of the present Thesis.

*Podophyllum Peltatum*, belongs to the natural order *Ranunculaceæ*, but some Botanists have assigned to it an order of which this plant is taken as the type, and accordingly termed it

Podophyllaceae.

The characters of the plant, according to Periera, are the following. — It has a long horizontal creeping perennial root, the stem is from eight to twelve inches high, naked with sheathing stipules at the base, dichotomous at the summit, dividing into two petioles, two to four inches in length, each bearing a peltate leaf. The leaf is large hang-  
ing, divided into five to seven lobes, cuneate, oblong, dentate, and often bifid at the apex. Flower is solitary in the axil of the petioles, peduncle recurved white. The fruit is an oval berry, one inch and a half long, smooth, yellowish when mature, succulent and pulpy having a mawkish sweet taste, edible but not agreeable. The plant flowers about the end of May or beginning of June, and ripens its fruit about September. The root or rather the rhizome is gathered in the month of August, after the leaves have fallen for then it is considered most active. — In the dried state and as imported for medicinal purposes, it presents the following characters. It varies from one to seven inches in length, about the size of a common goose quill externally of a redish, or dark brown colour, at

intervals presenting tuberosities, on the upper surface of which is left attached portions of the broken of aerial stem, and on the under surface the rootlets take their origin, - When the stem is cut across, it presents a large central medulla or pith, white in colour, and surrounded by a dark brownish line which separates it from the external whitish cortical portion.

The rootlets are all about the same size, averaging about that of a surgical probe, of a light greyish colour externally, smooth and breaking with a short smooth fracture, the transverse section presents a small brownish central medulla, surrounded by a large whitish cortical portion.

When chewed it is of a bitter taste, and causing when swallowed after a time fulness in the head, with slight frontal headache.

The rhizome has been repeatedly analysed. It was found by one observer to contain resin, starch, and a peculiar vegetable substance, crystallizable in white silky tufts. Another has found its constituents to be, albumen, gum, starch, extractive matters, lignin, gallic acid, fixed oil, traces of volatile oil, salts of potash, and lime, also

two resinous principles, one soluble in alcohol and ether, the other in alcohol only. - Both of these were found to possess purgative properties.

From the analysis and observations of Mr. Harvey Allan, it appears that the resin, which is soluble in ether, and which constitutes about four fifths of the whole resinous matters, is that which alone possesses any active purgative properties. The resinous matter thus obtained from the root has received the name of Podophyllin

Podophyllin, as obtained in commerce may be prepared in the following manner.

An alcoholic tincture is made by percolation; and the spirit afterwards distilled off till the residual fluid is about the consistence of treacle, The residue is then slightly heated, and poured gradually into water, kept during the period in a state of agitation. The mixture is then put by for twenty four hours, when<sup>it</sup> will be found to have deposited, a yellowish, or brownish white precipitate, this is then placed upon a calico-filter, and repeatedly washed with water, and then dried on paper at a very slow heat. According to Parrish the yield of Pod-

-phyllin as thus prepared is about three and three quarters per cent. The Podophyllin thus obtained is by no means pure. It is a powder varying from a dark brown to a yellowish or greenish tint. It is insoluble in cold, but slightly soluble in hot water, and almost entirely soluble in Alcohol and Ether. It has a bitter acid taste, and an odour somewhat resembling that of opium. When allowed to remain in cold water for forty eight hours it imparts to the water its bitter principle, but the resinous matter remains insoluble. Alcohol extracts both the bitter principle and resinous matters.

I made an infusion of the rhizome and rootlets of the Podophyllum, by macerating two drachms, in one ounce of water, containing two drachms of rectified spirit for fourteen days, and produced a solution of a slightly sherry wine colour, of an opiate odour, and bitter taste, and of an acid reaction. Tincture of Iodine caused a light red colour. A dose of thirty drops caused nausea sickness and depression, with some frontal headache, it did not produce purging. On adding to a fresh

fracture of the rhizome, a drop of concentrated sulphuric acid a yellow tinge was produced.

Nitric acid, caused the whole surface to become of a reddish brown.

Hydrochloric acid, a faint yellow, most distinct in the central medullary portion.

These three last tests will enable the physician or chemist to ascertain for himself the genuineness of the specimens <sup>of the rhizome</sup> he intends using.

### "Physiological Actions."

The leaves of the plant are said to possess narcotic properties; this I am not in a position to deny, but certainly the result of the only experiment I had it in my power to perform, would lead me to suppose them perfectly devoid of such effects.

I gave to a rabbit, two fresh leaves of the plant, and it eat them readily, suffering no evil consequences; this small quantity however did not by any means give them justice.

The resinoid principle of the rhizome, Podophyllin, acts as a cholagogue, and active purgative in man. It produces similar effects on the rabbit, cat, and dog. It acts

as a sialogogue in the Cat. and dog, & in doses of six to eight grains acts on the rabbit and cat as an irritant poison.

For the purpose of testing its physiological action, I gave to a rabbit each morning for four days in succession, one grain of Podophyllin, not seeing any appreciable effects produced, I gave to the same rabbit on the fifth morning five grains. This was given about ten o'clock A.M. about two hours after, it lay down seemingly quite helpless, showing evident symptoms of nausea, refusing all food when placed before it, and remained in this condition until three o'clock when I left it. On seeing it again in the course of two hours, found it lying on its left side apparently dead; a considerable amount of liquid faeces, and a copious secretion of urine occupied the bottom of the Box. On watching it more closely I observed a long convulsive gasp, which occurred every fifteen seconds. Pupils slightly dilated, but contracted slowly on exposure

to light, when the eye is touched, the eyelids remain unmoved, and when held up by the ears the animal does not struggle, but remains stiff as if dead. At six o'clock the respirations became less frequent, about seven or eight in the minute, slight convulsive movements of the extremities, the head is held back and the whole body is stiff. Supposing the animal to be dead, I was removing it to a table for the purpose of dissection, but was rather astonished when it gave another convulsive gasp; it now struck me that the podophyllin was acting narcotically, but whether I was correct in this supposition or not I leave to be judged by the appearances which the various organs presented on dissection. The animal remained in this, to all appearance comatose condition for an hour and a half, at the end of which time it was found to be dead, about nine hours and a half from the administration of the drug.

On dissecting the body of the animal immediately after, discovered the organs in following conditions.

"Thorax" The right lung was slightly expanded but the left was collapsed, both of a purplish colour.

"Heart:" The right auricle and ventricle were distended with venous blood, the pulmonary artery, together with the superior and inferior vena cava are likewise filled, and the left auricle and ventricle each contained a slight amount of semi-coagulated blood.

"Abdomen:" The stomach <sup>was</sup> is distended with flatus and a slight amount of semi-digested food. The small intestines in their upper third are filled with pure yellow-greenish bile, the lower two thirds are somewhat shrivelled in appearance. The liver is of a dark brownish colour, occupying the right hypochondriac and epigastric regions, the gall bladder is quite filled with secretion of bile, showing distinctly its pyriform shape.

The kidneys are slightly congested, and the urinary bladder, half distended with urine.

On opening the stomach, by incision along the inferior border, and allowing the contents to escape, found the mucous membrane con-

siderably corrugated, here and there at the pyloric orifice, and bet the greater and lesser curves, are visible distinct inflammatory patches. The duodenum is quite filled with pure biliary secretion.

The veins of the neck, internal and external jugular, are distended with blood.

On removing the skull cap, the venous sinuses are distended, the pia mater somewhat congested; nothing abnormal is seen on making a section of the brain.

The results then of this experiment, I think would tend to show, that the podophylin in grain doses, given at an interval of twenty-four hours, produced on the rabbit, little or no very manifest effects, but that a larger dose of five grains, given on a comparatively empty stomach, caused inflammation of the mucous membrane, acting as an irritant, increasing at the same time the function of the liver, and as I would suggest by a reflex act; and secondly paralyzing or more correctly producing a sedative effect on the heart's action, the circulation gradually becoming in

12.  
-peded, the respiration embarrassed, and life  
-terminating to all appearance in death by Coma  
"Experiment No. 11."

For the purpose of testing, whether or  
not the physiological action of the Podophyllum  
would be produced if absorbed by the blood.

I shaved the hair from the back of a rabbit  
made an incision about one inch in extent,  
and after dissecting up a flap of integument  
placed beneath it one grain of Podophyllum  
no effects being produced, on the following  
day I injected by means of <sup>Dr</sup> Wood's syringe  
twenty minims of a tincture of the strength of  
two grains to the drachm of rectified spirit, in  
the neighbourhood of both femoral veins, &  
also the same quantity into the cellular tissue  
of the neck, immediately over the Sternomast-  
oid muscle. I kept this animal living  
for twenty four hours more, then killed  
it, with a grain of strychnine.

On dissecting the thorax, the heart was found  
quite distended, both right and left auricles  
and ventricles being filled with blood (the effects  
of the strychnine). The lungs half expanded.

The liver darker in colour, than the first rabbit; the gall bladder also pretty well filled, but not nearly so decided as in Expt. No. 1. The upper part of the small intestine contained likewise about one drachm of bile, the large intestine filled with greenish faeces.

The Podophyllin in this experiment, did not seem to act so decidedly on the liver through the blood as in the other case when it was introduced into the stomach.

"Experiment No. III."

Podophyllin when given to a cat produces curious effects. The smallest particle when brought in contact, with the tongue of a full grown cat, caused at once a copious secretion of mucus and saliva.

I gave three successive doses in one week to the same animal, with like results.

Immediately after taking it, the animal sprang about, frothing at the mouth, which continued for fully half an hour. As soon as it attempted to swallow any food, the frothing at the mouth commenced followed by vomiting. On the last of the three occasions.

ions, the frothing and vomiting continued for fully two days, with intermissions, being excited, whenever the animal attempted to take any food.

I observed similar effects, were produced on a hen, when a grain of *Podophyllin* was placed on its tongue.

"Experiment No. IV."

Four grains of *Podophyllin* were given to a kitten, (one month old), and the effects produced were the following. Frothing and salivation immediately commenced, and continued for more than two hours, accompanied at short intervals by vomiting of mucus & frothy matters. Shortly after this, the animal began to show symptoms of pain, evidently abdominal, lay down on its side, and rolled about on the floor, mewling piteously; in the course of an hour or so, it commenced to gasp, lay still, & remained in this condition, until I left it for the night. On seeing it next morning at seven a.m. found it dead.

On dissection found the organs in the

Following conditions.

"Thorax":

Heart distended on right side, both auricle and ventricle being filled with venous blood. The right auricle and ventricle contained a small amount of coagulated blood.

"Abdomen":

The liver occupied the whole of the upper part of the abdominal cavity, of normal colour; on lifting up the left lobe found the gall bladder distended with bile, and also the bile ducts, the part of the duodenum over which the gall bladder lay was stained of a bright yellow colour.

The stomach was distended with flatus, and on opening found it contained about one drachm of watery fluid, like viscid mucus, on washing this out, the mucous membrane was seen distinctly congested, and more especially at the pyloric orifice.

The mucous membrane in this case was far more congested than in that of the rabbit, being of a bright red passing into a

pinkish tint; I think the reason of this was that the rabbit was allowed as much food as it could take prior to the administration of the Podophyllin, and in consequence <sup>the food</sup> had not the same opportunity of coming so immediately in contact with the mucous membrane, as in that of the unweaned kitten which was deprived of its mother's milk, for fully twelve hours, before the Podophyllin was given, and also during its action.

The small intestine contained fluid similar to that which was found in the stomach but were only slightly inflamed; the irritant action of Podophylline being apparently principally confined to the stomach. The large intestine contained a small amount of liquid. Kidneys, both right and left when divided, were undoubtedly highly congested, and I do not hesitate in stating my belief, that the Podophylline, acts on these visci, exciting their excretory function as it does on the liver, but not to such an extent; the urinary bladder was distended with urine.

I think the results arrived at in this last experiment, are that the Podophyllin acted first, as a sialagogue. Secondly, as an irritant poison, & thirdly, that death resulted in exhaustion, owing to the inflammation set up in the stomach & upper part of the small bowel.

The action of Podophyllin on the dog are in all respects similar to those which were produced in the Cat.

I placed about half a grain of Podophyllin, on the nose of a terrier, and immediately after on licking it off with its tongue, a copious frothy &ropy secretion of saliva, was discharged from the mouth, the animal walked backwards & forwards uttering every now & then a low growl, and tossing its head about, throwing the foam from it on either side, and conducting itself in a manner, not rendering its close proximity agreeable.

I did not manage to get the dog to take, a sufficiency of the Podophyllin to test its action as in the cases of the rabbit & cat.

18.

Without expressing any farther opinions regarding the physiological action of Podophyllin. I will now transcribe notes of Cases in which Podophyllin has been found to be of undoubted service.

The first case which I will mention is that of a man A - A. - aet. 28. who was admitted to the medical wards of the Royal Infirmary. (7<sup>th</sup> July /61) under the care of Dr. Beattie. Having charge of the case I give a brief outline of its history.

The Patient states that a year ago he had an attack of Jaundice, which came on gradually, that the icteric hue has never since left him, only varying in tint from time to time. Symptoms on admission. Skin over the whole body is of a yellowish tint, conjunctivæ likewise tinted, sweats a good deal, tongue moist & covered with a whitish fur, appetite impaired, bowels habitually constive, Liver considerably enlarged, & dense, Urine dark coloured & scanty, Breath of the patient characteristic of the hepatic odour. Prescribed the following. -

Recipe

Todophylline grana  $\text{ss} \times$   
 Extracti Cannabis Indicae  
 et Pulveris Zingiberis ana grana  $\text{ss} \times$   
 Fiat massa et divide in pilulas  $\text{ss}$ .

seq. Iij. una mane et nocte.

July 9<sup>th</sup> Bowels have been freely moved  
 thrice since yesterday, large quantity of bile  
 coming away at each stool, severe griping,  
 and scalding during defecation, urine increased.

July 10<sup>th</sup> The patient has taken two more  
 pills, but owing to the griping is ordered  
 to discontinue them. On examination find  
 the lower margin of the right lobe of the  
 liver more marked, & the viscus evidently  
 much diminished in size, from the action  
 of the Todophylline. The urine has also  
 increased in quantity.

The second Case was that of a  
 man, ætas 56, who was suffering from  
 "Cirrhosis"; he had been a hard gin drinker,  
 & came to the Infirmary principally on ac-  
 count of the œdematous condition of his

legs and feet, owing to obstructed portal circulation. He was commenced with the Podophylline, in the form of pill one grain to two of Extract of Hyoscyamus, and after taking 4 pills he expressed himself greatly ~~relieved~~ as well he may, since the Podophyllin did its duty, relieving the poor man of both his bile, confined bowels & ~~anæmia~~. This man complained much of nausea & griping.

The third case is that of an old man ~~ætas~~ 72. whose bowels had resisted all purgatives and had been constipated for the last 8 days. but who after taking one pill containing one grain of Podophylline experienced great relief by a free evacuation.

The Fourth case, was a Dispensary patient, a young married woman ~~ætas~~ 25. Nursing her second child. She had been seized with Hepatitis followed by an attack of Jaundice.

On seeing her I prescribed the following

R Podophylline grs IV  
 Ext. Hyoscyam. grs XVI.

Fiat massa et divide in ℞  
 pilulas octo. one night & morning.

To prevent griping I gave two grains of Hyoscyamus to half a grain of Podophyllin, as I found the Henbane more effectual in allaying the griping than Camalis Indica.

On seeing her next morning she had had a free evacuation twice, the faces were dark, & greenish, her urine dark of an indigo tint. She was ordered to take a pill every morning, and at the end of the week she felt herself quite better, although the jaundiced hue still remained.

This patient complained of little or no pain during the action of the Podophyllin, and I prescribed no other medicine with the exception of Henbane, so as to give the Podophyllin a fair trial, and am quite prepared to treat the next case that I attend in a similar manner, & so thoroughly convinced am I of the efficiency of the drug, as being an excellent cholagogue and quite free from the deleterious effects of Mercury. It acts without causing salivation, does not prevent the patient from engaging in his occupations whether in or

out of doors. The small dose which is requisite to cause purging is another circumstance in its favour when compared with Mercury which requires to be followed by either anauseous black draught, a couple of Colocynth pills or still more sickening dose of Castor oil.

The Fifth Case I now relate was also in Dispensary practice. The patient a married woman aged 35. states that she is naturally very bilious, is often seized with severe frontal headaches, heaviness over the eyes, & a feeling of weight in the epigastric region. only finds relief by encouraging vomiting with Mustard & warm water & applying Mustard poultices over the abdomen. her urine is scanty very drunly & dark. bowels invariably costive.

Previously to hearing of her case from a friend who had been attending her. I had been engaged in experimenting with Alcohol & rectified spirit on the Podophyllin, and had succeeded in making a tincture, composed of two grains to the ℥i of rectified spirit, 10 drops

of which I found produced slight laxative effects on my own person, and accordingly on going to visit this patient, took the pills with me, & ordered her to take twenty drops immediately being 11. o'clock a.m. Repeat the dose in the evening if she thought necessary.

On seeing her next day, she informed me that her bowels had <sup>twice</sup> operated freely, after taking the Lincture as directed, that the only inconvenience she experienced was slight nausea, headache relieved, & feeling of weight on stomach not so bad. I ordered her to take ten more drops in the evening. On seeing her next day, she expressed herself greatly relieved bowels had been purged twice or thrice very freely. Her urine had increased in amount.

A friend of my own, who had long had what he called his fortnightly bilious attacks, which generally lasted for two or three days, & consisting in frontal headaches, nausea, bilious vomiting, loss of appetite, and what annoyed him even more, accompanying attacks of loss of temper, (being at the head of a large whole sale business,

and inaptitude for his daily transactions; whenever he experienced the premonitory symptoms, he had recourse to his ordinary dose of five grs of Calomel with a double amount of Rhubarb. I got him persuaded to try the Podophyllin and made half a dozen pills, each containing half a grain of Podophylline one grain of Nuxvomica and one grain of Extract of Senna. I advised him to take one at night and another in the following morning. On returning one afternoon from his place of business, overcame with sickness headache &c he took two podophylline pills & went off to bed passed a restless night, as was usual with him, on such occasions, and at five o'clock a.m. he retched a considerable amount of pure bilious matter, after which he slept for three or four hours, and on waking took a tolerable breakfast, at two o'clock p.m. the tormina in the region of the Umbilicus commenced, followed in a short time by severe purging and scalding in the neighbourhood of the anus, an incredible amount

-out of bile was passed at each stool.

After this thorough scouring he expressed himself greatly relieved, and determined to avail himself of the Podophylline at his next attack, which however did not annoy him for fully six weeks after the one I have just mentioned, during the whole of which interim he had not the slightest derangement of health.

The symptoms of the second attack making their appearance, (in lassitude and headache) he at once took a single pill, and according to his own statement, felt the headache in the course of two or three hours lessened in severity, and altho' not having any appetite for food before going to bed, arose next morning quite refreshed & partook to his astonishment of a hearty breakfast, in the course of the evening the purging commenced but with very slight purging griping, & not so much bile as on the former occasion.

He now places so much faith in the Podophylline, as to keep beside him a

216.

boy of a dozen <sup>pills</sup>, one of which he takes at breakfast, if threatened with any attack & now attends to his duties, with greater comfort than he ever before experienced when trusting to the Calomel & Alubarb, ~~to~~ which days were what he termed his "shaky bluepill days"

There are a few more cases of a similar nature which I might relate, but I think that what has already been said, and with the testimony of Professor Miller, regarding its efficacy as a medicine with which he has kindly supplied me, nothing more need be said to testify to the excellency of Podophylline, not only as a thorough clearing out purgative, for it is more than a "persuader," but as a first class, if not the best Cholagogue we have in the Materia Medica.

It is unnecessary to quote the many authors who have published in the Lancet of last year, the high opinion which they each and all hold regarding the efficacy of Podophyllin - and accordingly

I close this short monograph, in transcribing Professor Miller's opinion.

He states. "That Podophyllin is a very certain purgative, - dose half a grain for an adult requiring to be combined with some anodyne Hemp. Henbane, or Belladonna.

In smaller doses it is good as an adjuvant to other evacuants. In a purgative

dose it is a most undeniable & infallible cholagogue - Also produces a thorough sweeping effect from the smaller bowels downwards. In smaller doses repeated every other day prevents formation of scybala, & assist in their removal when do form. Usually slow in its operation takes twelve to twenty hours before purges.

Its only disadvantage is that it is apt to cause nausea, sickness, & griping.

As I have stated the good qualities of Podophyllin, I must not forget to mention its bad qualities also,

~~It~~ Its action is variable; in some individuals, given in the ordinary dose of half

20.

Of half a grain, it not only purges but produces a certain amount of dysentery. In one case known to myself in which a friend, <sup>who</sup> was compelled to take a few drops of the Tincture I have formerly mentioned, suffered in the course of eighteen hours with an attack of Dysentery for which he could try nothing but the Podophylline. There are three cases told me by a medical man, in which Dysentery was produced by half grain doses.

Preparation. It is invariably prescribed in the form of pill, in half grain or one grain combined either with Hyoscyamus Hemp. or Belladonna. I have tried, & made fair trial of each of these anodynes, but think the best anodynes to combine with the Podophylline, are Hyoscyamus & Gentian one grain of each, & made up with a little powdered sugar. The Tincture which I made hardly deserves the name, strength of it being 8 grains to rectified spirit ℥ss, the whole of the drug is not however entirely dissolved by the spirit, a sediment being invariably left. It is of a dark, sherry colour, & of a disagreeable bitter taste.

29.

Twenty drops produces slight purging -  
but depends on the strength and age of the  
individual.

Another form in which Podophyllum  
has been prescribed, is by the form of sup-  
-pository, it is used with success in this  
way by Professor Simpson, in cases of  
of dropsy.

Francis M. Duncan  
3<sup>rd</sup> March 1863  
