A PHARMACOLOGICAL STUDY OF PHYTOLACCA.*

BY DAVID I. MACHT.[1]

INTRODUCTION.

The poke weed is a very common perennial plant in central and eastern North America, and indeed the largest herb known there. In the Southern States it frequently grows as high as 10 or 12 feet and nearly as broad. The purplish green stem is often several inches in diameter. The very long, thick and fleshy root resembles that of the horseradish and has therefore been the cause of numerous poisoning accidents, particularly since it has an acrid taste deceiving those unfamiliar with it. Europeans use the purple juice of the berries extensively for coloring their wines. Acids are employed to brighten this color, which changes to bottle green on addition of alkalis. The older generation of physicians used this perennial American plant as a medicine. It was official in the U. S. P., 1880 and 1890, and although no longer in the pharmacopœia is still described at the present time in the National Formulary and various dispensatories.

Preparations of both root and fruit of *Phytolacca* have been used therapeutically but the products of *Phytolacca radix* are considered more efficient. In the National Dispensatory the constituents of poke root are described as follows:

"The chemical composition of poke root is very peculiar. Its important active and poisonous constituent is an amorphous, bitter and acrid substance very similar to, if not identical with, saponin. This is probably the glucoside reported by Coscera. The alkaloid phytolaccin exists in very small amount. It occurs in white crystals, soluble in alcohol and somewhat in water, nearly insoluble in ether and chloroform. *Phytolaccic acid* is amorphous, soluble in water and alcohol, reduces silver salts and yields with earths and alkalis soluble salts, from which boiling hydrochloric acid separates the acid as a jelly. Sugars exist to the extent of nearly 10 per cent, and of starch there is an equal or greater amount. A little free formic acid, besides nearly 2 per cent of potassium formate, was obtained by Frankforter, as well as 6.2 per cent of calcium oxalate. The same chemist found more than 13 per cent of ash, nearly half of which was potassium oxide. The important constituent of the fruit, aside from the coloring matter, is phytolaccic acid. Various fruit-acids occur. The coloring matter is soluble in water, but not in alcohol, ether or chloroform. Phytolaccin is a tannin-like substance. The ash amounts to 8 or 10 per cent. The poisonous constituents of the fruit are apparently confined almost, if not wholly, to the seed."

The uses for which the dispensatories advocate this drug form a fantastic conglomeration of empirical indications impressing the modern pharmacologist as a complete reversion to the therapeutics of the Dark Ages. We read that the drug has been recommended as an emetic, purgative, a narcotic and a gargle and as a remedy for chronic rheumatism, granular conjunctivitis, ringworm and parasitic infections of the scalp and other skin diseases and for syphilis and cancer.

The writer has been unable to discover reports of any experimental pharmacological work on this subject. The only recent publication regarding poke root that he has found is an article of merely empirical and clinical character, entitled, "Poke Root in Medicine," by U. Aylmer Coates (*Am. J. Pharm.*, 93, 232 (1921)). Since our dispensatories, formularies and even pharmacopœias are still

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cluttered up with numbers of useless and often dangerous vegetable drugs, it was obviously worth while for the writer to make a study of phytolacca preparations to determine whether or not they exert any or all of the interesting pharmacological effects attributed to them. The fluidextract of poke root and fluidextract of poke berries (the former containing 40 per cent and the latter 26 per cent alcohol) were employed as a starting-point. In some experiments, the fluidextracts were administered as such. In others, as, for instance, in studies on isolated tissues, the alcohol was evaporated on the water-bath and the residue taken up in physiological saline to make up the original volume. Experiments were made on living plants, living animals and animal tissues.

Phytopharmacological tests, made according to methods described elsewhere by the author (1), were performed on seedlings of *Lupinus albus*, large variety, grown in physiological saline. The fluidextract as such was used in 1.0 and 0.5 per cent solutions and compared with control saline solutions containing, respectively, 0.5 and 1.0 per cent of 95 per cent alcohol. Even the dilute concentrations employed were markedly toxic for plant protoplasm. Seedlings grown in 1.0 per cent solutions gave a reading of 37 per cent while those grown in 0.5 per cent solutions yielded a phytotoxic index of 43 per cent.

When tested on animals and animal tissues, evaporated saline suspensions of *Phytolacca* were found to be very irritating. A drop or two instilled into the eyes of a rabbit produced marked reddening and irritation of the conjunctivæ. Similarly, one cc. of saline suspension, injected subcutaneously in rabbits and other animals, produced local infiltration and signs of painful irritation.

The toxicity of the saline suspensions was tested on goldfish, mice, rats, guinea pigs, rabbits and cats. Goldfish placed in water containing 1.0 per cent solution of fluidextract of *Phytolacca* in water keeled over on the side in 27 minutes. Arrest of respiration and death of goldfish occurred 40 minutes after their immersion in such solutions. Mice, intraperitoneally injected with as little as 0.25 cc. of such saline suspensions, died within a few minutes. The lethal intraperitoneal dose for medium-sized rats, weighing from 150 to 200 Gm., was one cc. The toxicity of such solutions was about the same for guinea pigs as it was for rats, computed on the basis of their relative weights.

Inasmuch as poke root has been recommended as a slowly acting emetic, cats were used in another series of experiments to investigate this particular effect ascribed to the drug. Administration by stomach tube of from 5 to 10 cc. of fluidextract of poke root diluted with water, was succeeded by repeated retching and violent vomiting, followed by prostration. This emesis was evidently not the result of any specific action on the vomiting center but rather a consequence of the gastro-intestinal irritation effected by the drug.

To ascertain whether any really narcotic action could be effected by small doses of the saline suspensions of the evaporated poke root extract, the writer made an experimental psychological study in which he employed methods described elsewhere (2). White rats, previously trained to run in the circular maze, were injected with small, non-toxic doses of 0.1 to 0.25 cc. of the suspensions and their subsequent behavior in the maze was carefully studied. No difference was noted in the rats' running time, the number of errors made and much less in their neuromuscular apparatus.

Studies were then made to determine whether or not poke root preparations are laxatives in the therapeutic sense of the word. Experiments were made on isolated intestinal loops from cats and rabbits kept alive in oxygenated Locke solution at body temperature. It was found that addition of saline suspension of poke root to the bath in which the intestinal preparation had been suspended produced no stimulation at all of the rhythmic peristaltic contractions. On the contrary, such saline suspensions of *Phytolacca* extract paralyzed the intestinal preparations. Occasionally this real paralysis of the smooth muscle was preceded by increased contraction due to irritating action of the drug. The paralysis of the tissue was proven by its failure to respond, after treatment with poke root or poke berry suspensions, to such specific stimulants of the intestine as pilocarpine, physostigmine or even barium chloride.

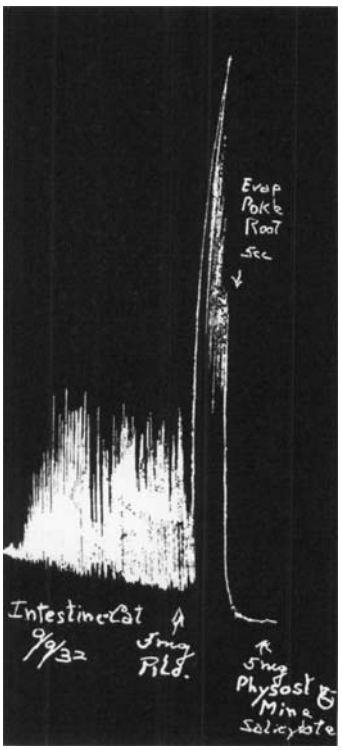

Fig. 1.—Small intestine of cat showing normal rhythmic contractions on very slowly moving drum. Powerful stimulation by 5 mg. of pilocarpine. Paralysis by 5 cc. of evaporated poke root extract in saline. Second dose of pilocarpine producing no response, indicates death of preparation.

In order to investigate the alleged laxative effect of *Phytolacca* extracts, the writer made another series of experiments on rats with emulsions of finely divided charcoal with and without the drug by a method described in detail elsewhere (3). Such tests revealed no difference between the controls and those rats which had been given *Phytolacca* emulsions in small quantities.

Inasmuch as empirical clinicians advocate the use of this drug in the treatment of chronic rheumatism, the writer deemed it worth while to investigate the possible antipyretic action of *Phytolacca*. Arthritis cannot be experimentally produced in animals. Even if it could be produced, it is practically impossible to study the effects of various analgesics on that type of pain in lower animals. It has been found, however, that antirheumatic drugs generally exert also an antipyretic action. Accordingly, fever was produced by injecting hay infusion in several rabbits. Before administration by stomach tube of a dose of *Phytolacca* extract and at various intervals thereafter the temperature of the rabbits was carefully measured. It was found that no antipyretic action was exerted by as much as 10 cc. of fluid evaporated extract of poke root in rabbits weighing 1.5 to 2 Kg. The following protocol serves as an illustration:

Gray rabbit weighing 2 Kg. 9:30 A.M., injected with 10 cc. of hay infusion. 12:00 M., temperature, 104° F.; 12:05 P.M., administered 10 cc. of evaporated extract of *Phytolacca*. 2:00 P.M., temperature, 104° F.; 3:00 P.M., temperature, 103° F.; 4:30 P.M., temperature, 103° F.

Control rabbit weighing 3 Kg. 9:35 A.M., injected with 10 cc. of hay infusion. 12:00 M., temperature, 104° F.; 2:00 P.M., temperature, 104° F.; 3:00 P.M., temperature, 103° F.; and 4:00 P.M., temperature, 103° F.

The effect of administration of one to ten cc. of saline suspension from the evaporated fluidextract of *Phytolacca* was studied on the kidney function of rabbits. The phenolsulphonphthalein renal test was employed in these experiments. Curiously enough, it was found that although the drug is irritant for the gastro-intestinal tract, even large doses of poke root or poke berry did not impair the kidney function.

Employing Rosenthal's bromsulphalein method (4), the writer also studied the effect of Phytolacca extracts on the liver function of rabbits. Five mg. of bromsulphalein per Kg. of rabbit were injected before administration of extracts and

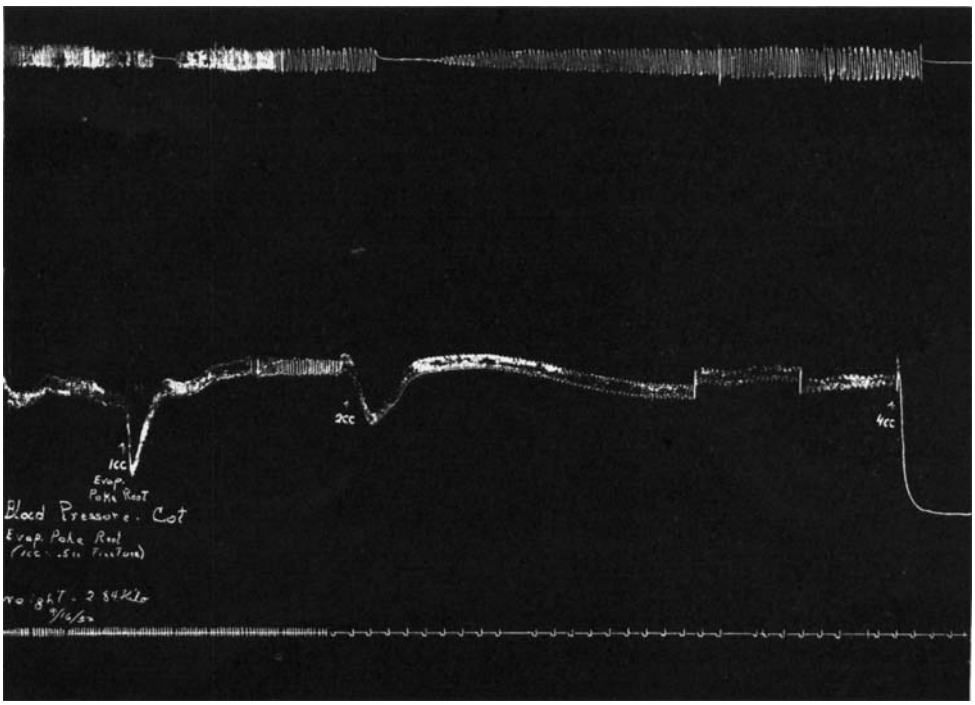

Fig. 2.—Blood pressure and respiratory curves of cat under ether anesthesia, showing effect of 1, 2 and 4 cc. of evaporated poke root extract injected intravenously.

after feeding the animal with the drug for periods ranging from one to three weeks, the liver function was tested again. Unlike the kidney function, the liver function was markedly impaired by *Phytolacca* feeding. The following protocols illustrate the effect of the drug on both kidney and liver function of rabbits:

RABBIT NO. 1, WEIGHING 2 KG.

Aug. 30	Kidney function test: phenolsulphonphthalein output in two hours (60% + 15%), 75%.
Sept. 6	Liver function test: bromsulphalein retention 15 minutes after injection, 5%.
Sept. 7	1 cc. of fluidextract of poke root, administered by mouth.
Sept. 8	1 cc. of fluidextract of poke root, administered by mouth.
Sept. 9	10 cc. of fluidextract of poke root, administered by mouth.
Sept. 13	Kidney function test: phenolsulphonphthalein output (75% + 10%), 85%.

Sept. 14 10 cc. of tincture of poke berry, administered by mouth.
Sept. 21 10 cc. of tincture of poke root, administered by mouth.
Sept. 22 Liver function test: bromsulphalein retention 15 minutes after injection, 10%.

RABBIT NO. 2, WEIGHING 2.5 KG.

Oct. 4 Kidney function test: phenolsulphonphthalein output in two hours, 80%.
Oct. 10 Liver function test: bromsulphalein retention 3 minutes after injection, 35%; 15 minutes after injection, 10%.
Oct. 13–25 Given fluidextract of *Phytolacca* in 5 cc. doses for ten days.
Oct. 27 Kidney function test: phenolsulphonphthalein output, 80%.
Oct. 28 Liver function test: bromsulphalein output 3 minutes after injection, 45%; 15 minutes after injection, 30%.

Finally, studies were made of the effect of *Phytolacca* solutions on circulation and respiration of cats under ether anesthesia. It was found that as little as 1.0 cc. of the evaporated fluidextract of the root, taken up in physiological saline and injected intravenously, markedly depressed the respiration and the circulation. Two cc. of the suspension paralyzed the respiration temporarily, and the animal slowly recovered. Four cc. simultaneously paralyzed both the heart and respiration.

COMMENT.

All the findings obtained in the experiments herein described are of particular interest when compared with the therapeutic claims for *Phytolacca* preparations found in the old textbooks and dispensatories. There is undoubtedly no rational basis for the employment of the drug in either syphilis or cancer or even in any other of the long list of ailments for which *Phytolacca* is recommended in those works. The drug is certainly a powerful irritant when administered locally and a violent poison when given internally in sufficiently large doses. It paralyzes the intestines and any purgative effect which may have been noted after its administration was doubtless but a manifestation of systemic poisoning. The vomiting produced by the drug is not the result of specific stimulation of the emetic center in the medulla but of intense irritation of the intestinal tract, as post-mortem examination of animals poisoned with large quantities of *Phytolacca* given by stomach tube has demonstrated. There is no experimental evidence to support the claims for its supposedly sedative or narcotic action on the neuromuscular system. Its vaunted tendency to reduce obesity may be ascribed to its general systemic poisoning of patients rather than to any specific action of the drug on the metabolism. *Phytolacca* has been recommended in the treatment of ringworm and other parasitic infections of the scalp, for which it may be effectively used, perhaps, but the writer is inclined to ascribe its action in such cases to the local irritation it produces and to the fact that it is a general protoplasmic poison. Poke root and poke berry preparations should therefore be considered as not only obsolete but dangerous.

SUMMARY.

1. A phytopharmacological study of extracts of *Phytolacca* was made on living plants and animals and on animal tissues.

2. The drug is very poisonous for seedlings of *Lupinus albus* grown in solutions of the respective extracts.

3. Small quantities of *Phytolacca* injected in rats trained in the circular maze produced no narcotic effect.

4. No antipyretic effect was noted after administration of the drug to rabbits.

5. The drug paralyzed smooth muscle preparations *in vitro* and had no truly laxative effect on the intestine *in vivo*.

6. Intravenous injection of saline suspensions of *Phytolacca* in cats produced marked depression and paralysis of both circulation and respiration.

7. These findings substantiate none of the claims made for the drug in the old textbooks.

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THE USE OF NEW SOLVENTS IN ALKALOIDAL ASSAYS.*

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I. SOLUBILITIES AND DISTRIBUTION COEFFICIENTS OF CERTAIN ALKALOIDS IN ISOPROPYL ETHER AND METHYLENE CHLORIDE.[3]

SOLUBILITIES.

The solubilities of strychnine, quinine, atropine and caffeine in isopropyl ether, methylene chloride, mixtures of isopropyl ether-methylene chloride, mixtures of ethyl ether-chloroform, mixtures of isopropyl ether-chloroform and mixtures of ethyl ether-methylene chloride were determined.

The method employed for these determinations was as follows:

Twenty-five cc. of the solvent were placed in a small bottle and enough of the alkaloid added to insure an excess after shaking in a mechanical shaker over night. The bottle was then placed in a thermostat bath, regulated at 25° C. to 0.1°, and allowed to remain in the bath for at least twelve hours in order that equilibrium between the solute and solvent would be reached. A volume of about 5 cc. was then pipetted off, placed in a tared weighing bottle and its weight recorded. The solvent was allowed to evaporate spontaneously, the residue dried to constant weight at 100° C., cooled in a desiccator over sulfuric acid and its weight recorded.

The bottle was again shaken for three hours in a mechanical shaker and a sample determined as before. This procedure was repeated until constant results were obtained which was usually after the second shaking.

The calculations were made upon a basis of grams of alkaloid soluble in 100 Gm. of solvent at 25° C. and in the cases of chloroform and ether the solubilities of the various alkaloids were calculated from solubility data given in the United States Pharmacopœia, X.

The accompanying tables (Tables I, II, III and IV) show clearly the solubilities of the above-mentioned alkaloids in the individual solvents and mixed solvents under consideration.

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