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ON THE

EFFECT OF OPIUM AND ITS DERIVATIVE ALKALOIDS.

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In the number of this journal for January, 1869, I recorded certain experiments which seemed to prove for pigeons an almost entire immunity from the influence of opium and morphia. Twenty-one grains of powdered opium, given internally; or, large doses of acet. opii under the skin; or, two grains of sulph. morphia used hypodermically, alike failed to produce any notable influence.

Repeating these experiments, Dr. B. W. Richardson, of London, attained similar results.

Two grains of acetate of morphia dissolved having been injected by this observer in three localities under the skin of a pigeon, the pupils were unaltered, the breathing somewhat slow and laboured, and the heart reduced in power. At the fifteenth minute slight emesis took place, and the temperature fell four degrees. For a half hour longer the bird seemed inclined to droop its head, but no further phenomena due to opium were perceptible.

In a second experiment a pigeon took on the first day 21 grains of solid opium; on the second day, 30 grains; on the third day 40 grains, and on the fourth 50 grains in one dose. The temperature did not fall one degree, and no other symptoms of poisoning occurred.

Dr. Richardson, after thus fully confirming my results, makes certain suggestions, pointing out the direction which should be followed in pursuing this research. These concern the relative susceptibility of other and especially carnivorous birds, the capacity of other alkaloids to poison pigeons, and the reason why they escape the usual effects of opium. Some of these questions I had already set myself to answer, and, in the course of inquiry, others arose of equal or greater interest, and are more or less sufficiently replied to in the present paper.

The amount of opium which a pigeon may swallow without loss of life is so great as to enable me to assert that it is next to impossible to kill

it in this manner. Dr. Richardson has compared in the following passage the relative susceptibility of the pigeon and the child of one year old.

"It is clear," he says, "that a pigeon can receive at once as much opium as would produce dangerous, or even fatal symptoms, if divided equally and administered to twenty children under one year old, the weight of the bird itself being at least fifteen times less than that of each child, or 200 times less than the combined weight of the children.

"*Expt.*—In February, 1869, desirous of learning whether it was possible to kill the pigeon with ingested opium, I chose a large bird, two years old, and gave him every day ten grains of aqueous extract of opium, night and morning, sometimes while fasting, at others during digestion. This was the daily equivalent of 40 grains of ordinary opium, so that at the close of eight days the bird had taken 320 grains of opium. During the following week I gave twenty grains of extract twice a day in bolus; more or less of this was vomited, but many doses were retained entire, and the pigeon had thus disposed in this one week of 280 grains of extract of opium. To sum up, in one fortnight, this bird ate much as usual; had its bowels relaxed somewhat, and vomited more or less, but showed no signs of coma, narcotism, or any muscular or sensory disability whatsoever. During this time it took in all 420 grains of aq. extr. opii—equal to 840 grains of opium."

I considered it useless to continue the experiment. Since this time I have occasionally given larger single doses, but nearly always they were partially gotten rid of by vomiting, either very soon after administration, or, as happened sometimes, twenty-four hours later, a fact which of itself proves how very slowly the poison is absorbed, and points thus to one of the elements which combine to protect the pigeon from fatal injury.

Expt.—July 20. I gave, by the mouth, 40 grains of aq. extr. opii at 3.23 P. M. July 21, at 2.20 P. M. while being handled it vomited about one drachm of brown fluid containing opium in large amount. During this twenty-four hours it was without food, but supplied with water. I should add that it also vomited 18 grains of like fluid an hour after it was first given. This was restored to the stomach, and no emesis occurred afterwards until the next day. It recovered without any symptoms of opium poisoning.

I next desired to learn whether the immunity, which seemed to be entire as regards ingested opium, was as complete when morphia was thus used. Accordingly—

Expt.—I gave a pigeon 7 grains of sulphate of morphia dissolved, by the mouth, at 5.20 P. M., July 13. For several days there was a slight but unusual tendency to crouch and keep still, but absolutely no other symptoms. The evacuations were healthy, or rather loose. Complete recovery.

Expt.—July 14. At 4.20 P. M. I gave, by the mouth, 12 grains of sulphate of morphia, dissolved in acidulated water. Held in the hand for half an hour; the pigeon trembled excessively and exhibited nausea. At 5 P. M., crouches; 5.40, pupils respond to light and dilate in the dark. July 15, 4 P. M. Found dead and rigid. Evacuations abundant.

Similar experiments were made with 1, 3, and 5 grains, but in no case did death occur. In another experiment 9 grains failed to kill, and a repetition in another pigeon using 14 grains caused death during the following night.

It thus became probable, first, that as regards poisoning with morphia internally, there is some individual difference among pigeons, irrespective

of age; second, that the immunity is not absolute when morphia is ingested; and third, that as large a dose as 12 grains may be needed to insure death. It is possible that a smaller amount might, in rare cases, destroy life, but as the following observation proves even 12 grains may fail to secure this result.

Expt.—July 23, 3.05 P. M. My assistant, Mr. Landis, gave a pigeon, by the mouth, 8 grains of dissolved sulphate of morphia. At 3.30 it vomited a few drops, and at 4.30 took four additional grains. On the 26th it was well, lively, and particularly quarrelsome, and on the 30th was still in perfect health.

A second series of experiments were directed towards discovering what amount of morphia might kill when used hypodermically. As regards this point, I was surprised to find that wide differences were visible in different pigeons. This was partly due to various and easily seen causes, but in part also to reasons which probably rest on the idiosynerasies of the birds employed.

Thus, pigeons of two or three months old were commonly killed by injections into the groin of half a grain to one grain, but sometimes, though rarely, survived two grains. The same amounts used under the skin of the back were much less fatal.

Older birds of the second year, as in Dr. Richardson's experiments and my former ones, were rarely killed by doses under two grains in the groin. I find recorded but one death from one grain, while the escapes from this fate are rare in pigeons which have received in the groin more than three grains. The present series of observations, therefore, show a singular range of susceptibility, and indicate very distinctly that, as regards hypodermic injections, the pigeon enjoys no such complete immunity as seems to obtain with opium given by the mouth, while as compared to morphia internally administered, the hypodermic method is vastly more fatal.

The phenomena of opium, or rather morphia poisoning in birds, are extremely interesting, from the absence of nearly all of the symptoms which are usually supposed to characterize this mode of death. My observations were made upon pigeons, chickens, and ducks, and lead to the belief that the latter two are nearly as difficult to poison as the pigeon. Unfortunately, I have been unable to secure any purely carnivorous bird with which to follow out one of Dr. Richardson's suggestions.

It is singular that birds should have been so rarely used as subjects on which to study poisons. Flourens has some almost forgotten cases of the poisoning of little birds by opium, with certain symptoms and pathological appearances such as I have never met with in larger birds. I mention them at some length in a note,[1] not having been able to repeat them in the same species as he employed.

[1] My friend Dr. William Pepper assures me that he saw a large cockatoo survive unharmed an accidental dose of eight grains of aq. extr. opii.

M. Flourens' experiments are somewhat surprising. He used sparrows chiefly,

When a lethal dose of morphia is put in the groin of a pigeon, the bird seems unaffected for a few minutes or longer, and then tries to find a corner as far as possible from observation. Presently its gait becomes unsteady, and the tail is twitched up at intervals in an uncertain fan-like movement, or the wings stir in abrupt, short jerks. An increasing awkwardness follows, till at length the bird falls, and then, or while still erect, is seized with general convulsions, between which the breathing is seen to be very laboured. Meanwhile the darkened mucous surface of the mouth and larynx show how the blood is suffering, and at length it dies suddenly in violent convulsions. In no case have I seen sleep precede death, nor in any have I observed well-marked constipation. I have measured the pupils many times without noticing any such changes as opium causes in man. It may not be uninteresting to add that atropia, either in the eye, or given internally, has on the pigeon's iris no visible influence, except in some profound poisonings, to cause a curious swift alternate contraction and dilatation within a very small range of movement.

In birds, as in mammals, morphia lowers the temperature when it acts at all as a poison. The occurrence of convulsion not only checks this fall, but may suddenly elevate the column to the normal standard or even above it. No mode of exercise seemed competent to produce in the healthy pigeon a rise of more than one and a half degrees, but when opium had lowered the general temperature, then a convulsion was able to send the mercury up three to five degrees, so that, in some instances, there was the anomaly of the pigeon dying, with a temperature above that it possessed before being poisoned.

The following selection from the records of a large number of experiments may suffice to illustrate the symptoms just described :—

Expt.—July 19. Pigeon, second year, rectal temp. $109\frac{1}{10}^{\circ}$ F., received in groin at 4.10 P. M., two grains of dissolved sulphate of morphia. Within one minute appeared unsteadiness of gait, the fan-like flirting motion of the tail, and soon positive rocking forward, with slightly laboured breathing. At the 20th minute, an effort to use the thermometer excited a great deal of struggle.

and found that one grain of aq. extr. opii caused the bird to fall into a *stupor* at the close of fifteen to twenty minutes. At first light and easily interrupted, it became at last so profound that neither noise nor light availed to awaken him. Birds affected walked when pushed, flew when cast in the air, and on being let alone, took anew the attitude of deep sleep, the head turned beneath the wing. Larger doses produced convulsion and death, and the author found in a large number of cases, an effusion of blood between the two cranial tables, which, in small birds, can be seen to form during life. This symptom is also said to occur in pigeons, nor, according to Flourens, are these exempt from the phenomena observed in smaller birds. The text of this passage is somewhat dubious, but seems to be intended to describe as identical the signs of opium poisoning in pigeons and sparrows. I confess myself unable to reconcile the statements of this eminent physiologist with those made by Dr. Richardson and myself. Are pigeons different in France and in America?

The temperature was noted as 111⅖°. Fortieth minute, symptoms the same, temperature 109⅕°. The pigeon was now released and chased about, when the temperature was found to be 110⅘°. Sixtieth minute, remained seated, gasping somewhat; slight general tremor; neck muscles weakened and respiration more difficult; temperature 109⅕°. Convulsions at 64th minute, consisting in alternate motion of the two wings, and also of the two legs, with flexion of the toes. These spasms were brief, and not violent. During the intervals, a loud sound seemed to excite sudden and abrupt movements in the wings. Unable at this time to stand at all. At the 70th minute, temperature 109⅗°. The pigeon fell into a general convulsion of great violence, which passed into others of less severity at very short intervals. Death occurred at the 80th minute, the thermometer marking a rectal temperature of 113⅖°. Post-mortem rigor began in one minute in the legs.

Expt.—Pigeon; received in groin five grains of sulph. of morphia at 4 P.M. The symptoms were, in succession, uncertainty of movement, with jerking motions of wings, tail, and legs, increasing by laboured breathing; the darkened mouth of asphyxia; at length, unable to stand, convulsions, general in character, with flexion of the toes, and not tetanic in type. Meanwhile, continued fall of temperature, with a rise of over three degrees during the final and fatal convulsion.

If, now, this curious rise of temperature be due to the heat evolved during the excessive and morbid exercise of the muscles in spasm, it must be sufficient to overcome, and more than overcome the tendency to loss of temperature owing to poisoning by morphia. Other and very different causes connected with the vaso-motor nerves may be also at work; but, at all events, the subject would repay close study.

Thus far my observations exhibit a very striking uniformity of symptom among the pigeons studied. Always there were unsteadiness, laboured breathing, increasing signs of apnœa, unaltered pupils, and finally general convulsion and death. In no instance was there any true hypnotic effect.

The influence of opium and of morphia salts upon the domestic chicken and duck were also studied; first, with a view to learning whether these, like pigeons, were difficult to poison; and secondly, what were the symptoms caused by lethal doses.

Expt.—Sept. 15. A large cock chicken received in the thigh 1 grain of dissolved sulphate of morphia. No effects were visible.

On Sept. 17, five grains similarly employed produced no notable symptoms.

Sept. 20. A cock chicken received, subcutaneously, in the groin, ten grains of sulph. morph. at 2 P. M. At 3.30, is inclined to stand still; mouth remains open, respiration quick and laboured. Eyes shut; rocks on his feet, and inclines to fall backward. Finally crouches, and at times makes ineffectual efforts to stand, being occasionally successful, and again sinking suddenly on his breast. He is now, 5 P. M., extremely feeble, the eyes being shut, and the head swaying to and fro; frequent watery stools. At 5.30 same condition. The next day he was well and fed eagerly.

Sept. 22. I injected into the breast and two thighs of this same bird twenty grains sulph. morph. Injection occupied five minutes. Released at 2.15 P. M. He ran to a dirt-pile, and scratched in pursuit of food. At the 8th minute signs of distress appeared; eyes shut, mouth gaping, unsteadiness on feet. 2.45. Crouches. 3.20. Unable to stand when pushed or teased; occasional convulsive starts. 3.40. Restless, frequent starts; watery stools; eyes unaltered; breath laboured. At 4.7, sudden and violent convulsion, with legs rigidly extended. The fit lasted a few seconds, and was followed by quietude, now and

then broken by spasmodic extensions of the legs, the bird lying on his side and uttering a curious note like a faint bark. 4.9. Convulsion as before. 4.12. Lies on side; frequent spasms of legs in extension, the head remaining at rest, and the wings merely twitching; respiration gasping in character, and death at 4.14, without other symptoms.

Expt.—A hen took, by the mouth, thirty grains of extract of opium without visible after-effect.

Expt.—In this case, the exceptional excitement of brain by opiates was noticed, and a range of symptoms somewhat unlike those which we commonly see in the chicken. A hen received in thigh ten grains of sulph. morph. at 4.23 P. M. At 4.25 became unsteady; mouth open, respiration irregular and laborious. 4.29. Crouches. At 4.55, somewhat better. Took, by mouth, 100 drops acet. opii. At 5.10, after having been tranquil and sleepy, eyes shut, and standing up, had a period of what looked like delirium with vertigo. He ran to and fro, and at last rotated to the left for half a minute. Presently this passed off, and at 5.30, had a second turning fit. After this he was sensitive to light and sound, and at one time as if half asleep, and presently again excited, and furiously attacking a duck. After this the rotations were frequent. They began with a cry and a ruffling up of the neck feathers. At 5.36, violent turning, after which he crouched; but at 5.40 he was evidently weak, and the turnings became converted into swift shuffling to the left. Then he fell on the left side and had twitchings of feet and wings, synchronous with the laboured breath, the head jerking incessantly. At last he had a single general convulsion, ending in death at 6 P. M. Rigor in the legs set in within one minute.

Expt.—A large duck showed no evidence of poison from six grains of morphia at one time, and nine at another a week later. Ten grains thrown into the groin caused emesis in one minute. After 40 minutes he was so little influenced, that I gave in like manner twenty grains. In two minutes he crouched, unable to stand, and showed great distress in breathing. In a few minutes he rallied, and, when walking, would fall suddenly, his legs slipping out apart from one another. Then he began to twitch all over, uttering an incessant quack, and at the 68th minute fell in violent tetanoid convulsion, the feet extended, the head thrust out. The fit ended in sudden death.

I have also examined the effects on birds of some of the rarer alkaloids of opium. In order to enable observers to compare my observations with those made upon mammals, I have exacted from each specimen of the alkaloid used a rigorous identity, in chemical reaction with that employed by Dr. Harley. I found the need for precaution in one specimen of Thebaia (Paramorphia), which gave altogether different results from a second supply. (For the latter, and for the most courteous interest in my investigation, I have to thank Messrs. Powers & Weightman). Of cryptopia, the latest discovered of these bodies, I have been able to get but a small specimen, amounting to one grain—a fact which I greatly regret since reading Dr. Harley's very interesting account of its physiological effects.

Narcotina seems to have been omitted by Dr. Harley in his examination of the opium alkaloids, for what cause does not appear. By many authors it is classed as inert. Orfila found that thirty grains were required to kill a dog, but it has been given by Dr. Garrod to man in doses of thirty grains, and was reported by him and O'Shaughnessy to be merely tonic and anti-periodic. Doses of 120 grains are said to have been given to man without effect.[1] I have taken narcotina several times, in doses of

[1] Gmelin, Handbook of Chem., vol. xvi. p. 137.

5, 10 and at last 30 grains with no result save some slight gastric embarrassment which may possibly have been due to other causes. The specimens used by me were two in number. The first, indicated as No. 1 narcotina, was made by Powers and Weightman. The second, similarly distinguished as No. 2 narcotina, was manufactured many years ago by Robiquet, Boyveau & Pelletier. Both gave the usual chemical reactions.

Expts.—Narcotina was given to pigeons by the mouth in powder or dissolved in acids, in doses of two to six grains, but without obvious effect.

Expt.—To a large pigeon, five grains of narcotina No. 2, dissolved, were given subcutaneously at 4.26. Temp. of rectum 108°. Within four minutes some twitching of the tendons of the feet was visible, giving rise to slight unsteadiness of gait. At the 5th m. nausea and vomiting; 7th m. moves about in an excited way, then suddenly has retraction of head, difficulty of breathing, and successive general convulsions. The effect on temperature was in this case remarkable, because, despite continued convulsions rarely interrupted during half an hour, the mercury fell to 96° F. five minutes before death, which took place at the 84th minute.

Post-mortem examination.—The right heart was still acting, and all the muscles appeared to be irritable. In another case, three grains, by the groin, and five of No. 1 narcotina by the crop, caused death within twelve hours.

Expt.—One and a half grains of No. 2 narcotina dissolved in water and sulphuric acid, and put under the skin in three places, caused, in thirty seconds, excitement, feebleness, convulsions of tetanoid nature, irregular respiration, and death in ten minutes.

In many instances pigeons escaped death after hypodermic doses of two grains, but very generally such amounts produced feebleness, unsteady gait, and early convulsions, depending less than in morphia upon the previous induction of apnœa. None of the birds were affected with stupor, and in all the tendency to convulsion was the predominant symptom.

The facts I have here recorded are among the most curious which have fallen under my notice in the course of this inquiry. That a drug which is apparently incapable of killing man should be so fatal a convulsivant to the bird appears to me most remarkable, and as contrasted with the opposite case of opium, a poison for man, and with difficulty hurtful to the pigeon in any mode of administration, the toxic energy of narcotina must certainly be regarded as among the most singular facts in toxicology.

Thebaia.—This alkaloid, some times known as Paramorphia, corresponded absolutely as to chemical reactions with that used by Dr. Harley. It was made by Powers & Weightman, of Philadelphia. The tetanizing action of this agent has long been known ; a dog, according to Harley, has been killed by two grains used hypodermically, and mice perished from the use of $\frac{1}{12}$ to $\frac{1}{20}$ of a grain. It proved speedily fatal to pigeons, causing terrible tetanic spasms as related in the two following experiments :—

Expt.—A pigeon received in the groin one grain of paramorphia partially dissolved. At the close of a minute the pigeon was seemingly unaffected. But suddenly fell into the most terrible tetanic spasm, the feet thrown out, the head turned back and twisted to the left. The wings merely quivered a little, the legs being most affected. So intensely violent were the spasms which succeeded, that while they endured, respiration was altogether impossible. Death occurred in two minutes.

Expt.—A pigeon received in the groin one-third of a grain of paramorphia dissolved in thirty mm. of acidulated water. Vomiting occurred within a few seconds followed by sudden and violent tetanic convulsions, with scarcely an interval of repose until death took place at the close of one minute and thirty seconds. In these spasms the limbs were extended rigidly, the spine bent, the tail turned up, the head thrown back and twisted almost completely around so that the beak pointed towards the tail.

Comparing these with cases of strychnia poisoning, I have been unable to detect any essential difference. The tetanic spasm, a tendency to which is exhibited by birds to which narcotina has been given, finds here in poisoning by thebaia a perfectly typical presentation, while, as we have seen, a likeness to the strychnic spasm may be sometimes observed in the deaths of birds poisoned by morphia.

Meconine.—This alkaloid, prepared by Rosengarten & Sons, responded to all the usual chemical tests. Dr. Harley states that he is unaware of any observations upon its toxic action, and quotes Orfila to the effect that three grains thrown into the jugular vein of a dog produced no ill results.

Dr. Harley ascribes to it slight tranquillizing and hypnotic effects when placed under the skin in doses of one to two grains, but saw no such influence from the ingestion of five grains. I myself have taken first two and on another occasion six grains suspended in cold water without effects of any perceptible character, and since birds are not put to sleep by the other opium derivatives, I was prepared to find no result from meconine, which is only slightly soluble in water at the normal temperature of the pigeon.

Expt.—Eleven grains of meconine were made into pills with soap and given to a pigeon at 4.10 P. M. Vomiting took place in a few minutes and repeatedly afterwards for two hours. No other symptoms were noted.

June 17. Six grains, partially dissolved and in part suspended, caused vomiting when ingested, but gave no other evidence of activity.

June 16. Twelve grains administered in the same way produced no other result.

I suspected that the irritation of stomach might be due to the presence of the needle-like crystals of this alkaloid, for which chloroform alone is a perfect solvent. At all events its difficult solubility must render it very slow of absorption; and, in this as in other like cases, may interfere to prevent the exhibition of symptoms which might be observable if we possessed a solvent vehicle capable of readily conveying it into the blood.

Expt.—In three instances I placed under the skin in a state of partial solution in hot water, 3, 8, and 12 grains of meconine. The injections were made with a hypodermic syringe, armed with a tube large enough not to be clogged by the fine crystals. The alkaloid was fully dissolved in boiling water, which was allowed to cool to 100° F.—the fluid being constantly stirred so as to insure the precipitating crystals being as small as possible. At first I thought that the agent thus used tranquillized my pigeons, but further observations showed this tendency to repose to be due rather to the desire of a pigeon so wounded to remain at rest than to any toxic power of the salt employed.

No convulsive symptoms occurred in any case, and as I have said no conclusive signs of stupor appeared.

It thus appears that meconine is only emetic when given to birds by the mouth, that it has no perceptible power to hypnotize or to excite the brain

or spine when used under the skin, and that six grains of it taken internally by man have no appreciable influence.

Codeia, considered by Magendie to be a hypnotic and stupefier, and to be for these purposes half as strong as morphia, has also been examined of late by Harley. This latter observer[1] (p. 169) seems to have some doubt as to the codeia used by M. Bernard, and refers to a statement made by himself, p. 141 of his treatise, for the reasons justifying this doubt. On referring to the page in question I do not find, however, any such explanation, except as regards narceine.[2] At all events, my own codeia, made by Rosengarten & Sons, answers to all the requirements of Dr. Harley's identifying tests. Bernard considers it as a hypnotic when given to dogs in doses of $\frac{1}{77}$ gramme; but Harley finds that in doses of two or three grains hypodermically employed it causes only depression of the respiratory system and of the cardiac function, and a latent tendency to convulsion. In the mouse it produced like results, ending in tetanic convulsions and death. In four to five grains it causes in man some disposition to sleep, but never occasions in these amounts any decided effects of this character. Like morphia, it at first raises the pulse, contracts the pupil, and very often gives rise to gastro-intestinal derangement. I have myself taken five grains in one dose after failing to secure marked results from two grains. The former dose was taken fasting. In an hour the pulse had risen 20 beats per minute, and I felt slight giddiness, nausea, and a sense of heaviness about the head without any remarkable desire to sleep. These symptoms slowly passed away, leaving me with a sense of gastric oppression for two or three days.

These observations scarcely prepared me for the powerful influence which codeia exerts on pigeons.

Expt.—I placed under the skin in three localities seven grains of codeia dissolved in water, with the aid of nitric acid. Before I could set the bird at liberty violent convulsions came on, ending in death within one minute. These spasms were not tetanic.

Expt.—One grain dissolved was used under the skin of the groin. When released the pigeon moved about in what seemed to be a delirious restlessness, but which in a few moments was clearly made out to be the state of muscular

[1] The Old Vegetable Neurotics, by John Harley, M. D. London, 1869.

[2] I quote from a letter of Dr. Harley to me, dated Nov. 1, 1869, the following remarks, which serve to clear up the matter spoken of in the text: "First as to Bernard and codeia. My reasons for referring to p. 141 to show that the codeia used by him was doubtful, was as follows: Bernard there says that narceine is more valuable than codeia. At p. 142 of my work, I show that what we English call pure narceine is one of the most insoluble constituents, not only of opium, but of the whole vegetable kingdom. Where shall we find another substance that is neither soluble in water (for water which only dissolved $\frac{1}{400}$th part can hardly be called a solvent) nor in alcohol, nor ether, nor chloroform? Turning to codeia (p. 160) we find it soluble in 25 parts of water and in 40 of ether, while it is miscible in almost any proportion with alcohol and with chloroform. If Bernard could say that narceine was more soluble than codeia, what was I to think of his codeia on the one hand, and of his narceine on the other? for as soluble bodies they seem to me the exact antipodes of each other."

irritability which precedes convulsions. The bird shifted about uneasily, flapping his wings and stamping his feet in incessant motion. This was followed, or rather this increasing passed into general convulsions, with flapping of the wings, jerking of the head, and alternate flexure and expansion of the feet and toes, until death took place in three minutes.

Expt.—Half a grain of codeia produced like results, and death in eight minutes.

These, with other observations, enable us to draw a distinct line as to convulsing energy between this drug and morphia, since doses of the latter agent not exceeding a grain, often allow of escape from death, and even larger quantities only effect destruction to life after a far greater lapse of time.

Narceine.—In regard to this substance, there seems to have been a certain confusion which must have arisen from the employment by various observers of substances which under one name possessed different qualities, both physical and physiological. Claude Bernard looks upon narceine as superior even to morphia in its somniferous power. He states also, that it is free from any convulsivant or excitant action, and that animals killed by it die in a state of muscular relaxation, such as I have never found to occur with pigeons under any of these agents.

The French and German observers generally regard it as a gentle hypnotic. Dr. Harley is distinctly of opinion that the drug used by Bernard was not pure narceine because of its far greater solubility in water than the alkaloid described by Pelletier and recognized as narceine in England. Dr. Da Costa appears to have had similar doubts, and Mr. T. Smith, of Edinburgh, informs Dr. Harley that meconine which separates with narceine may give it the appearance of increased solubility.

I have taken it myself (Merck's narceine) in doses of one-half a grain up to five grains. The latter dose alone produced any effect. It was taken dissolved in warm glycerine—two drachms with one drop of sulphuric acid. An hour after taking it I felt a slight headache and sense of constriction, but observed no change in the pulse or the respirations. I was doubtful as to whether or not it caused any hypnotic effect, and conclude, therefore, that it can hardly be very powerful. I had no dysuria. How to explain the discrepancy between such facts as this and others of like nature observed in my own practice or that of Dr. Da Costa, I do not see, unless by supposing, with Dr. Harley, that the alkaloid as furnished varies remarkably. In his hands this agent was found to be a gentle hypnotic, but owing to its insolubility unfitted for hypodermic use.

The great therapeutic importance recently assigned to narceine by Bernard, and supported by the clinical observations of Bèhier and others, induced me to examine the alkaloid with unusual care. I have studied specimens from three distinct manufacturers, and regret having been unable to add one of French origin. I give in tabular shape the appearance, colour-reactions, and relative solubility of each make of narceine.

Physical Characters.

No. 1.	No. 2.	No. 3.
E. Merck.	Powers & Weightman.	Foreign, of Unknown Make.
"Compressed asbestos-like mass of soft acicular crystals, very light and colourless."—Harley.	Like No. 1, but slightly tinted with pink, probably an accidental impurity, more loose in texture and more bulky than No. 1.	Like No. 1.

Solubilities.—No. 1. Merck's is soluble in 1000 parts of distilled water at 60° F.

No. 2. Powers & Weightman's dissolves in 4000 parts of water at 60° F.

No. 3. Foreign, maker unknown, imported by Bullock & Crenshaw, soluble in 2100 parts of water at 60° F.

No. 1. Merck's narceine is wholly soluble in 95 parts of water at 212° F., and begins to precipitate at 175° F. At 140° F. a large part has separated from the solvent.

No. 2. Powers & Weightman's is dissolved by 300 parts of water at 211° F., and begins to precipitate at 160° F. At 90° F. not one-half has separated.

No. 3. Procured from Bullock & Crenshaw; maker unknown; is dissolved by 175 parts of water, at 212° F., and begins to precipitate at 190° F.

Dr. Harley's narceine, made by the Smiths (Edinburgh), or by Morson, was more soluble than any of my specimens. One part was soluble in 100 of water at 212° F., and in 400 parts of water at 60° F. Bernard's narceine was made by Merck, of Darmstadt; by Menier, of Paris; and with unusual care by Guillemette, of the same city. This correspondence in the make of the substance between his narceine (Merck's) and mine still further complicates this puzzling question.

I give next the colour tests which are less reliable for identification. It is to be regretted that Bernard does not supply either these or the solution tests.

Colour Tests.—Hydrochloric acid, sp. gr. 116, diluted five times with water gives with

No. 1.	No. 2.	No. 3.
A fine blue.	A fine blue.	Dissolves without colour.

All the specimens dissolve in the pure acid without colour.

Nitric acid gives

No. 1.	No. 2.	No. 3.
Orange yellow,	Orange yellow,	Orange yellow,

with aqueous solutions. A morsel of narceine let fall on a drop of the pure acid gives a yellow centre and orange edges.

SO_3 dissolves all three of the specimens with a deepening amber hue, which becomes greenish-orange in Dr. Harley's narceine, as in all of mine, and finally takes a port-wine red. On heating, it then becomes chocolate-brown with a purplish tint. On adding 100 parts of water, fine brown flocculi are seen, and an excess of potassa at length throws down, in his case "a quantity," in mine a moderate amount of dark brown flocculi, the proportion varying in the three specimens, but in all leaving above a colourless fluid.

The great discrepancy as to solubility, and in one case as to one of the colour tests, makes it difficult to conceive of the various specimens as being identical in chemical construction. I have tested all three on myself, in doses varying from two to five grains, without any notable result.

The three following observations represent the influence of this drug upon the pigeon.

Experiment.—Two grains of narceine, Merck's, were dissolved in 30 mm. of hot glycerine with one drop and a half of chlorohydric acid. The solution was clear on cooling. It was injected into the two groins in three localities. There may have been some slight difficulty of breathing within a few hours, but no other result.

In two others I used four grains hypodermically, employing the other specimens of narceine, that is Nos. 2 and 3, but was unable to observe any marked result.

Since the date of these observations I have repeatedly injected five to six, and once nine grains of narceine, dissolved in acidulated glycerine, but, except the often noted tendency to rest quiet in a corner, no symptoms of moment were seen.

In the confusion which at present obtains in regard to the various manufactures of narceine, I am unwilling to draw any very absolute conclusions, but it certainly appears that the agents employed by Harley and myself must be different from that used by Bernard. Perhaps it were safe at least to assert that some of my specimens must represent a large percentage of narciene, or may indeed be pure, so that in any case we may confidently conclude that narceine is among the lowest of the opium alkaloids in its power to produce convulsions, the pigeon being taken as the agent most susceptible to this form of toxic impression.

Cryptopia, the last discovered of these numerous and interesting bodies, has been examined physiologically, or rather clinically, for the study was not a full one, by Dr. Harley, who considers it to be a cerebral excitant, and to a less degree an hypnotic. In large doses it dilates the pupil, and as a somniferous agent is regarded by Dr. Harley as being twice as active as meconine or narceine, and one-fourth as powerful as morphia.

I have been able to secure but one grain of cryptopia, but as this was of the make of T. & H. Smith, the discoverers, I considered it to be identical with Harley's. The small amount of the drug in my possession necessarily limited my experiments.

Expt.—One-fifth of a grain of cryptopia used under the skin of a pigeon caused nausea and efforts at emesis in five minutes. At 15th minute the bird appeared to be weak, and the breath was long and laboured. It was seemingly well next day, but was found dead on the morning of the third day. I had of course a good deal of doubt as to this result being due to the cryptopia, and these doubts were strengthened by the absence of any more marked results in a second pigeon, which received subcutaneously half a grain, and did not die.

Since reading the first proof of this paper, I have to thank Dr. Harley for a larger amount of cryptopia, and to express my regret that it came too late to admit of my adding any new experiments.

Porphyroxin and *papaverine*, which complete the list of alkaloids of opium, I have been unable to procure. These various agents possess, as has long been known, very diverse effects. Taking morphia as an ex-

ample, in some persons it causes only cerebral excitation with delirium and insomnia. In others it affects chiefly the spinal centres, occasioning nausea and emesis of obstinate character, while in very rare instances, one of which was illustrated recently in the person of a physician of this city, it produces tetanoid symptoms. More commonly it brings on sleep, but these influences may coexist in various degrees in the same person, or one or two only may be perceptible.

Dr. Harley has pointed out the fact, that in different animals one or other of these effects largely predominates, and has thus illustrated anew the necessity of studying every poison on numerous classes of animals, a precaution upon which I have more than once insisted. My present research still further emphasizes the need for an enlarged method of study.

In all of the animals examined by Dr. Harley, sleep was produced, though with an amount of difficulty, and from quantities of morphia largely varying in the several cases, while in the mouse and the horse, the action of this drug on the spinal centres was probably more notable than in man. A comparison of these results with those which I have obtained in birds, is alike interesting and instructive. We have in the latter a class of beings which, for reasons presently to be stated, are practically incapable of being poisoned by the ingestion of opium, and which are affected only by enormous doses of morphia. Where the latter has been given in sufficient amount, we have, up to the moment of convulsion, absolutely no induction of sleep or stupor, neither do we observe any loss of sensation, general or special, but the heart is quickened, and respiration made laborious, by the influence of the poison upon the respiratory centres. The convulsions which precede death seem to be sometimes due to asphyxia, and are then incessant up to the moment of death, while in others they seem to be due merely to a general excitation of the motor ganglia, since they occur at intervals, with periods of comparative freedom intervening.

Neither can I agree with Baxt or Bernard in regarding the convulsions caused by morphia as being always tetanic in character—a point, however, on which I shall have further occasion to dilate. In birds, then, morphia acts with difficulty, causes no sleep and no delirium, and strikes chiefly the motor and spinal centres, affecting very early the respiratory ganglia, and to a certain extent depressing the temperature. There is one reason for this marked influence on breathing, which is explicable by certain peculiarities of the respiratory organs. In man and mammals generally, the motor nerves of respiration leave the spine high up in the cervical region, and the essential fibres run a short course to their respective muscles. In birds, however, the respiratory organs extend into the lower belly, and the movements of this part, as well as of the regions above it, seem necessary to sustain life. The nerves of respiration emerge at various points all the way down to the lower dorsal vertebræ, and a cross section of the spine anywhere above this point causes sudden death. The large number and

great length of these nerves have probably something to do with the readiness with which the breathing becomes embarrassed, with the prominence, in a word, of this symptom.

M. Bernard has divided the effects of the various opium alkaloids into three classes, soporific, convulsive, and toxic; one or other of the three being predominant in the case of each of these agents, but not of necessity to the exclusion of the other two. M. Baxt in like manner arranges them under the two heads of convulsives and narcotics, while Harley is disposed to consider that all of them are alike excitant, and hypnotic in varying degrees. Each of these observers may be absolutely right as regards the physiological reactions of the alkaloids in question, considered with reference to certain animals, but the attempt to apply their conclusions broadly so as to include birds, only serves to show the great necessity for caution in all such deductions.

Let us compare the results obtained by Bernard and Baxt with my own, premising that as yet, with the exception of morphia, these alkaloids have never been as thoroughly studied as belladonna or woorara, and that neither Bernard's classification, nor Baxt's, nor mine, is more than a mere toxicological sketch.

M. Bernard believes, as I have said, that the opium alkaloids have three properties or powers: 1. Soporific; 2. Excitant or convulsing; and 3. Toxic. He classes them thus in the order of their power.

Excitant or convulsive agents.—1. Thebaine. 2. Papaverine. 3. Narcotine. 4. Codeine. 5. Morphine. 6. Narceine.

Soporifics.—1. Narceine. 2. Morphine. 3. Codeine. The three others have no soporific force.

In capacity as poisons, viz., toxics.—1. Thebaine. 2. Codeine. 3. Papaverine. 4. Narceine. 5. Morphine. 6. Narcotine.

What strikes us most about this arrangement is the want of relation between toxic power and capacity to convulse, as instanced in the position of narcotine, and the high place as a soporific assigned to narceine.

Waldemar Baxt, quoted in *American Journal of Medical Science*, October, 1869, regards the opium alkaloids as either narcotic or tetanically convulsive. In narcotic energy, he arranges them thus: 1. Papaverine; 2. Morphia; 3. Narceia; 4. Codeia; etc. As convulsives thebaine stands first, porphyroxin second, narcotine third, codeia fourth. Dr. Harley's view of the matter from this standpoint varies from that of Bernard or Baxt, and there are so many discrepancies among the three observers as to indicate the need for a still further examination of the subject. For reasons already pointed out, I have limited my own experiments to birds, and despite the statement of Bernard as to the power of morphia, codeia, and narceia, to produce in pigeons and sparrows the forms of sleep which he regards as peculiar to these drugs, I have been unable to detect anything in this direction, beyond a slight tendency to

quietude, which we can never be sure is not due to the habit of the wounded or sick pigeon of seeking a remote corner and remaining at rest.

As regards power to stupefy, I can therefore make no classification. My experience with cryptopia has been too limited to allow of any positive conclusion. All but two of the other alkaloids examined by me cause convulsions, but thebaia alone appears to be truly a tetanizing poison, although in the duck, and rarely in the pigeon, morphia caused spasms, which may be termed tetanoid. Thebaia stands highest in rank as a convulsant, and is followed in order of power by narcotina, codeia, and morphia, meconine and narceine having no such influence. In this arrangement of narcotina I agree with Bernard and Baxt. Neither of them makes mention of meconine, which Harley regards as distinctly hypnotic, but which is almost without influence in the pigeon, even when given in enormous doses.

My own arrangement of the relative poisoning power of the substances we are considering would be as follows :—

1. Thebaia ; 2. Codeia ; 3. Narcotina ; 4. Morphia — Meconin and Narceina being too innocent for addition to the list. It will of course be remembered that this statement applies only to birds, and chiefly, indeed, to pigeons.

The conclusions which I have finally reached in regard to the influence of opium alkaloids on birds are as follows :—

1. Birds : namely, ducks, chickens, and pigeons, are never poisoned by crude opium, its aqueous extract, or acetum opii (black drop), given internally ; while the salts of morphia must be given in enormous doses to produce fatal effects when administered in the same manner.

2. Morphia salts, used hypodermically in excessive amounts, never cause sleep or stupor, but act as excitants (convulsants) upon the motor centres. In some instances, the spasms are tetanoid in character ; but in the duck they approach nearest to the typical strychnic spasm.

3. Thebaia is a tetanizing agent, only inferior in energy to strychnia and brucia.

Narcotina, almost inert in man, destroys birds when employed hypodermically, in doses of from 2 to 7 grains.

Codeia is a fatal convulsing agent in birds (pigeons).

Meconin causes emesis when given internally, and is harmless if placed under the skin.

Narceia has no perceptible influence, except to disturb slightly the respiratory function.

Cryptopia in doses of $\frac{1}{5}$ to $\frac{1}{2}$ gr. has no effect.

None of these agents cause sleep in the pigeon, duck, or chicken.

The inaction of ingested opium is due, as I believe, to two causes.

First, to the very great slowness with which it, as well as morphia, is

absorbed. This is shown by the fact that, twenty-four hours after a full dose has been given, the pigeon may vomit it in large quantities. In a few cases, the greater bulk of what I had given was thus rejected; but in many others all was retained.

The remaining amount of protection necessary to constitute an insurance against fatal results, must be due to the great difficulty with which pigeons, especially old birds, are poisoned by opiates. Probably elimination is sufficiently rapid to protect the system against a dangerous accumulation of the drug; but since the feces and urine are evacuated from a common cloac, I have been unable to study the rate of excretion in a satisfactory manner.

Pigeons, and probably other birds, seem to possess the same peculiarity which causes certain men to exhibit, under opiates, only excitement of the motor ganglia, emesis, and a restlessness, which, with fuller doses, might possibly eventuate in convulsions—a rare incident of opium poisoning, which, however, occurred early in a case that I have elsewhere reported. The normal sleep of these birds is not nearly so profound as that of man; and, on the other hand, their motor nerve system enjoys the faculty of evolving an enormous amount of force, and, as compared to their cerebral manifestations, is far more prominent. It is possible that we may discover that equivalent doses may affect more profoundly, in the direction of stupor, the creature taking them in proportion as its cerebral development is greater and its brain more active. Such, at least, seems to be the probable conclusion from a general survey of the effects of morphia on various classes of animals; while, especially in mammals, it will, I think, be discovered that individual peculiarities come in to modify the result, as they never so distinctly or so frequently do in the lower grades of animal life.

I had suspected that the enormous respiratory apparatus of birds might have some share in protecting them from opiate poisons; and this may possibly be the case, but I may add that I have failed to make it sure by the aid of experiment. An elaborate series of nearly an hundred experiments were made, to discover whether oxygen gas would increase this protection, and whether a small percentage of carbonic acid in the air breathed would plainly destroy it, and cause to be fatal doses which are not otherwise lethal. The great labour thus expended failed to afford any other than a negative result, and only left it clear to me that the inhalation of oxygen does not protect the system which has been attacked by morphia.

I have once again to repeat my thanks to my assistant, Mr. Laudis, for the industry and accurate care with which he aided me in the conduct of this research.