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"On the Physiological Action of the Chinoline and Pyridine Bases." By John G. M'Kendrick and James Dewar, Edinburgh. Communicated by J. Burdon Sanderson, M.D., F.R.S. Received June 11, 1874*.

It is well known that when either quinine, cinchonine, or strychnine is distilled with caustic potash, each of these substances yield two homologous series of bases, named the pyridine and chinoline series. It has also been shown by Anderson and Greville Williams that bases isomeric with these are obtained by the destructive distillation of coal or from Dippel's oil. Greville Williams has also pointed out that chinoline obtained from coal-tar differs in some respects from that got from cinchonine. It would be a subject of physiological interest to ascertain (1) the physiological action of the various members of the series; (2) whether there was any difference in this respect between the members of the series obtained from cinchonine and those got from tar; and (3) whether, and if so, how, both as regards extent and character, the physiological action of these bases differed from that of the original alkaloidal bodies. We have for some time been engaged in this research; and the results we now beg leave to lay before the Society.

I. Method of the Research.

The bases in both series are difficult to separate from each other; but this has been done, as far as possible, by repeated fractional distillation. The substance first examined was chinoline obtained from cinchonine. It was employed both as sulphate and hydrochlorate, dissolved in water, and introduced by subcutaneous injection into the animal. The strength of the solution employed in this and in all other instances was one part of the base to twenty parts of water. Its physiological action was tested on frogs,

* Read June 18, 1874. See 'Proceedings,' vol. xxii. p. 432.

mice, rabbits, guineapigs, cats, dogs, and man; but as the effects were found to be similar in all of these instances, the majority of the observations were made on rabbits. After having noted the effects of chinoline, we next studied, by the same method, the action of hydrochlorates of the bases distilling off at higher temperatures, including such bases as lepidine, dispoline, tetrahiroline, &c. We then examined the pyridine series, beginning with pyridine itself, and passing upwards to bases obtained at still higher boiling-points, such as picoline, lutidine, &c. Lastly, the investigation was directed to the action of condensed bases, such as dipyridine, parapicoline, &c.; and the effects of these substances were compared with those produced by the members of the chinoline series and among themselves. So far as we could observe, there was no difference as regards physiological action between bases obtained from cinchonine and others got from tar.

II. Physiological Effects of Hydrochlorate of Chinoline ($C_9H_7N\,H\,Cl$).

The administration, by subcutaneous injection, of $1\frac{1}{4}$ grain for every 1 pound of weight into a healthy rabbit produced the following effects:—In four or five minutes the animal appeared to become drowsy, was unwilling to move; but when pushed, locomotion was not affected. Both the pulsations of the heart and the respiratory movements were slightly increased in frequency at this stage. The drowsiness increased, and in a few minutes more the animal sank on its abdomen and remained motionless, with the eyes widely opened. It was now gently turned over on its back or side, and it remained in that unnatural position. Still later, there was complete anæsthesia. At no period was there any hyperæsthesia. Reflex functions were also in abeyance so far that they could not be excited by pinching or pricking, but irritation by a Faradic current caused feeble movements. The animal appeared to be unconscious of loud sounds. The pupil was normal as regards size, and it contracted readily when exposed to a strong light. The reflex movements of the eyelid were not lost until the animal was in a state of deep stupor from an overdose. The respirations were now much fewer in number, and of less depth than normal. The heart still acted vigorously, but the pulsations were decreased in number by about one sixth. After remaining motionless in that condition for a period of three or perhaps four hours, the rabbit slowly recovered, raised its head from the table, began to move about, and frequently ate food placed before it. It recovered completely from the dose above indicated, without any bad symptom supervening. A dose of 2 or $2\frac{1}{2}$ grains per pound weight was usually lethal. If, at the end of three hours, the animal showed no indications towards recovery, it apparently sank in a state of profound insensibility, the heart-pulsations became feebler, and the respirations more and more shallow, until they were barely perceptible. Death ensued

without convulsions. The temperature of the body fell 6° to 8° below the normal. An examination of the body, made immediately after death, showed the following appearances :—(1) The vessels on the surface of the brain were somewhat congested; the substance of the brain itself did not exhibit any increase of vascularity; (2) the lungs were congested, more especially along the borders; (3) the heart was in a state of diastole and full of dark-coloured blood; (4) the veins in the mesentery and the larger vessels on the intestine were much congested; (5) the liver showed numerous minute ring-like congestions, indicating congestion of the portal system; (6) the kidneys and other abdominal and pelvic viscera were normal in appearance; and (7) the urine in the bladder contained no albumen or sugar.

From these symptoms and *post mortem* appearances, and from special methods of experiment, we draw the following conclusions regarding the action of hydrochlorate of chinoline.

1. *Action on the Nervous System.*—The action is chiefly, if not altogether, on the nerve-centres, and not on the nerves or on their peripheral terminations. When the sciatic nerve is irritated by very feeble Faradic currents, it manifests no diminution of sensibility, and the muscles supplied by the nerve contract with apparently their normal energy. The nerves of a frog killed by hydrochlorate of chinoline show all the properties of nerves obtained from a non-poisoned animal. The sympathetic system of nerves is not usually affected to any appreciable extent, as evidenced by the normal condition of the pupil, the absence of dilatation of the vessels in the ear (consequent on paralysis of the vaso-motor system), and by the fact that, in an animal deeply under the influence of chinoline, the phenomena following section and irritation of the sympathetic in the neck of a rabbit take place to the same extent and in the same order as in a non-poisoned animal. In several instances we have observed dilatation of the vessels of the ear and slight contraction of the pupil; but these, from their rare occurrence, appear to be exceptional. No change was observed in the action of the pneumogastric nerve, so far as could be ascertained by the effect on the heart produced by Faradic irritation of that nerve. We have observed no symptoms leading us to suspect irritation, or paralysis, of the centres in the cerebellum, or in the ganglia at the base of the brain; but in lethal doses the respiratory centres in the *medulla oblongata* become gradually affected, as shown by the diminution of the respiratory movements both in force and frequency. The motor columns of the spinal cord do not lose their power of conduction from the encephalon to various parts of the body, because, on irritating with a weak Faradic current the end of the cord in a rabbit decapitated while deeply under the influence of the substance, powerful convulsive movements ensued. The reflex activity of the cord is much weakened, inasmuch as it cannot be excited by pinching or pricking; but it is not entirely lost, because it may be excited by Faradic stimulation; and it has

been observed in several experiments that strychnine, subcutaneously injected into a rabbit prostrate with hydrochlorate of chinoline, is followed by its usual physiological effects. It appears, therefore, that the substance acts chiefly on the sensory and motor centres in the cerebral hemispheres, weakening or removing all consciousness of external impressions and also all voluntary acts.

2. *Action on the Respiratory and Circulatory Systems.*—In the first instance the action of the heart and the respiratory movements are increased, but afterwards they are much diminished, and death appears to be the result of these processes becoming weaker and weaker, until they cease altogether. The increased action observed, at first, is probably due to the excitement of the animal consequent on the injection of fluid beneath the skin. So soon as the substance acts through the blood on the nerve-centres, the action of both systems is weakened. We regard this weakening as due to an action on an encephalic centre, for the two following reasons:—first, because irritation of the sympathetic and pneumogastric nerves in the neck of a rabbit, completely under the influence of hydrochlorate of chinoline, produces acceleration and retardation of the heart's action respectively, as occurs in a healthy animal; and secondly, when the heart of a frog was treated, according to Coats's method, with serum containing 3 per cent. of chinoline, no effect was observed. These experiments seem to indicate clearly that the substance acts on the encephalic centres, and through them on the heart and respiratory organs. The action of the heart finally ceases, probably by its textures being supplied with only venous blood.

3. *Action in lowering the Temperature of the Body.*—It was found, in three instances in which minute differences of temperature were observed at intervals of one minute, during a period of one hour before and one hour after the subcutaneous injection of hydrochlorate of chinoline, that the substance produced a gradual and uniform fall of temperature to the extent of from six to eight degrees below the normal. In all of these instances the animal recovered from the effects, and, during recovery, the temperature slowly rose to its normal limit. This action we regard as of considerable importance. It is probably to be explained by interference with nutritional changes between the blood and the tissues, and also by the diminution, both in frequency and depth, of the respiratory movements.

III. Action of Hydrochlorates of the Higher Bases of the Chinoline Series.

1. *Bases obtained by distillation between* 200° *and* 280° C. *Lepidine &c.*, $C_{10}H_9N$.

These bases produced the same general action as chinoline, with the exceptions (1) that the dose required to produce a state of complete stupor was somewhat smaller than in the case of chinoline, and (2) that,

after a state of stupor had been produced, the animal was less likely to recover, while it was observed that, frequently, before death, there were jactations of one or other of the limbs and convulsive twitchings about the mouth.

2. *Bases obtained by distillation between* 280° *and* 300° C.
Dispoline &c., $C_{11}H_{11}N$.

It was now observed that the symptoms following subcutaneous injection were considerably different from those of chinoline. One grain for each pound weight of the rabbit produced, in about five minutes, apparent uneasiness, side to side movements of the head, with a tendency occasionally to move backwards. This condition continued for three or four minutes, when the animal lay flat on its abdomen with its legs outspread. It was not in a state of complete unconsciousness. There was no anæsthesia. In several instances there were compulsive twitchings of the limbs, grinding of the teeth, and a slight tendency to opisthotonos. The lethal dose was smaller than in the case of chinoline. The effects were a longer time in appearing, and they had more of a spinal than of a cerebral character.

3. *Bases obtained by distillation above* 300° C.
Tetrahiroline &c., $C_{12}H_{13}N$.

These were found to be still more active. A dose of $\frac{3}{4}$ of a grain per pound weight produced, in eight or ten minutes after it had been subcutaneously injected, violent convulsions, and was almost invariably fatal. During the first five minutes after the introduction of the poison, no marked symptoms were noticed. At the end of this time, the animal became uneasy, ran forwards in an excited manner, and then fell over on its side. The convulsions which ensued were similar to those produced by the action of large doses of quinine or cinchonine. They did not resemble the tetanic spasms produced by strychnia, as they were not excited by peripheral irritations; but they had an epileptiform character, consisting of irregular jactations of the limbs, crunching of the teeth, movements of the eyeballs, pawing movements of the fore limbs, &c. The animal seemed to be semiconscious throughout. It was still susceptible to pain.

A consideration of the effects just described indicates that, as we ascend from the lower to the higher members of the chinoline series of bases, the physiological action becomes modified as follows:—

1. The action on the sensory centres of the encephalon becomes less marked, until in the highest group there is no unconsciousness, but only slight stupor.

2. The actions of the motor centres of the encephalon and spinal cord are not affected in the lowest group, but become gradually more and

more involved as we proceed upwards, until, in the highest group, we have substances producing powerful convulsions.

3. The lethal dose is smaller for the higher than for the lower members of the series.

IV. Action of Hydrochlorates of the Bases in the Pyridine Series.

The physiological action of the bases of the pyridine series was next examined in the following order :—

1. *Pyridine*, C_5H_5N.

The hydrochlorate of this base produced no effects, even in doses of 6 grains per pound weight, other than slight excitement and acceleration of the pulse and of the respiratory movements. The animal, judging from its gait and demeanour, appeared to be in a state analogous to intoxication. It recovered without any bad effects.

2. *Picoline*, C_6H_7N.

The substance was employed both in the form of the base dissolved in water and as a hydrochlorate. The salt was found to be more active physiologically than the base, but the kind of action was the same. The general effect was to produce, with a dose of 3 grains per pound weight, in the first place, general excitement and a full bounding pulse. This state was followed by a drowsy condition, which did not pass, with even a dose of 6 grains per pound weight, into complete stupor. The rabbit could always be readily aroused. While in the drowsy condition, the pulse fell in frequency and volume, and the respirations became feebler*.

3. *Lutidine*, C_7H_9N.

The effects were similar to those produced by picoline, only more marked. A dose of 3 grains per pound weight produced deep stupor, from which the animal could not be aroused. It remained in this condition for a period of from two to three hours. The pulsations of the heart were much reduced in volume, but only slightly in frequency; but it was clearly observable that the respirations were much less deep than in the natural condition, and they were reduced in frequency by about one third. In a case of death from a lethal dose of 4 grains per pound, there was venous congestion in all parts of the body, but the heart was still feebly pulsating. It was observed that the blood had a peculiar dark chocolate-brown appearance. Examined with the spectroscope, it showed the two bands of oxyhæmoglobin.

* The results we have obtained differ considerably from those described by H. Vohl and H. Eulenberg in their paper on the "Physiological Action of Tobacco when used as a Narcotic, with especial reference to the Constituents of Tobacco-Smoke," Archiv Pharm. [2] cxlvii. 130–166.

4. *Collidine*, $C_8 H_{11} N$.

Collidine was still more active in its effects. With a dose of $1\frac{1}{2}$ grain per pound weight, the animal rapidly sank into a state of profound stupor, from which it could not be aroused. Anæsthesia was complete. The pulsations of the heart and the respirations became more and more feeble, until death ensued in about 20 minutes after the dose, apparently in consequence of failure of respiration. There were no twitchings or convulsions. The subcutaneous injection into a rabbit of 1-80th of a grain of strychnine was followed by the usual physiological effects of that substance.

5. *The Higher Pyridine Bases obtained by distillation above* 200° C., *such as Parvoline*, $C_9 H_{13} N$, &c.

These were found to be still more active; but the effects were of the same nature as those just described. The lethal dose was found to be about $\frac{3}{4}$ of a grain per pound weight. In two or three minutes the animal sank on its abdomen; when pushed could move with difficulty; respirations were rapid and irregular. It then lay on its side, and in four or five minutes died, apparently in an asphyxiated condition. There were no convulsive spasms or twitchings. This substance was lethal in much smaller doses than the lower bases of the chinoline series.

The pyridine series of compounds thus showed a gradual increase in activity of physiological action. The lowest of the series produced merely excitement from irritation of the encephalic nervous centres, while the highest produced paralysis of these nervous centres. There was no irritation of the spinal cord causing increased reflex activity. Death ensued from gradual failure of the respiratory movements leading to asphyxia. The action of the higher pyridines was thus somewhat analogous to the lowest of the chinoline series, with this exception, that the pyridine compounds tended to cause death by asphyxia. It is to be noted also that the higher bases of the pyridine series were lethal in somewhat less than one half of the dose required to destroy life by the lower members of the chinoline series.

V. Action of Hydrochlorates of the condensed Bases of the Pyridine Series.

Considering the close analogy in chemical composition between the polymeric bases of pyridine and certain natural bases, such as nicotine, it became of importance to examine the physiological action of these bases, which were prepared, according to Anderson's method, by the action of sodium on pyridine, picoline, &c. The following were the effects observed after the subcutaneous injection of 1 grain per pound weight into a rabbit:—The animal remained quiet for a period varying from four to eight minutes, when it suddenly appeared uneasy, ran forwards as on tiptoe, with the back arched, and, falling on its side, became

violently convulsed. The convulsions continued, almost without intermission, for three or four minutes, when death ensued. So far as could be observed, consciousness was not lost until immediately before death. The character of the convulsions resembled that of those produced by cinchonine or quinine, except that the tendency to backward movements, with the fore legs extended, was not so marked; they also resembled those produced by salts of the higher members of the chinoline series, but they were more severe than in the latter. The hydrochlorates of two condensed bases of this kind were employed—the first made from pyridine, and the other from picoline. The formulæ for these are:—hydrochlorate of dipyridine, $C_{10}H_{10}N_2$ 2HCl; and hydrochlorate of dipicoline, or parapicoline, $C_{12}H_{14}N_2$ 2HCl. The latter was found to be the more active of the two, but the actions were identical in character.

VI. General Conclusions.

1. There is a marked gradation in the extent of physiological action of the members of the pyridine series of bases, but it remains of the same kind. The lethal dose, however, becomes reduced as we rise from the lower to the higher.

2. The higher members of the pyridine series resemble, in physiological action, the lower members of the chinoline series, except (1) that the former are more liable to cause death by asphyxia, and (2) that the lethal dose of the pyridines is less than one half that of the chinolines.

3. In proceeding from the lower to the higher members of the chinoline series, the physiological action changes in character, inasmuch as the lower members appear to act chiefly on the sensory centres of the encephalon and the reflex centres of the spinal cord, destroying the power of voluntary or reflex movement; while the higher act less on these centres, and chiefly on the motor centres, first as irritants, causing violent convulsions, and afterwards producing complete paralysis. At the same time, while the reflex activity of the centres in the spinal cord appears to be so far inactive as not to be excited by pinching or pricking, it may be readily roused to action by strychnine.

4. On comparing the action of such bases as C_9H_7N (chinoline) with $C_9H_{13}N$ (parvoline), or $C_8H_{11}N$ (collidine) with $C_8H_{15}N$ (conia from hemlock), or $C_{10}H_{10}N_2$ (dipyridine) with $C_{10}H_{14}N_2$ (nicotine from tobacco), it is to be observed that, apart from differences in chemical structure, the physiological activity of the substance is greater in those bases containing the larger amount of hydrogen.

5. Those artificial bases which approximately approach the percentage composition of natural bases are much weaker physiologically, so far as can be estimated by amount of dose, than the natural bases; but the kind of action is the same in both cases.

6. When the bases of the pyridine series are doubled by condensation, producing dipyridine, parapicoline, &c., they not only become more

active physiologically, but the action differs in kind from that of the simple bases, and resembles the action of natural bases or alkaloids having an approximately similar chemical composition.

7. All the substances examined in this research are remarkable for not possessing any specific paralytic action on the heart likely to cause syncope; but they destroy life, in lethal doses, either by exhaustive convulsions or by gradual paralysis of the centres of respiration, thus causing asphyxia.

8. There is no immediate action on the sympathetic system of nerves, although there is probably a secondary action, because, after large doses, the vaso-motor centre, in common with other centres, becomes involved.

9. There is no appreciable difference between the physiological action of the bases obtained from cinchona and those derived from tar.

The physiological action of the substitution derivatives of these substances will be related in a further communication.

March 4, 1875.

JOSEPH DALTON HOOKER, C.B., President, in the Chair.

The Presents received were laid on the table, and thanks ordered for them.

The Right Hon. Sir Stafford H. Northcote was admitted into the Society.

In pursuance of the Statutes, the names of the Candidates for election into the Society were read as follows:—

William de Wiveleslie Abney, Capt. R.E.
William Archer, M.R.I.A.
Edward Middleton Barry, R.A.
James Risdon Bennett, M.D.
Dietrich Brandis, Ph.D.
Charles Orde Browne, Capt. R.A.
George Buchanan, M.D.
Walter Lawry Buller, Sc.D.
James Caird, C.B.
John Casey, LL.D.
William Chimmo, Capt. R.N.
Latimer Clark, F.R.A.S.
Cuthbert Collingwood, M.A.
George Critchett, F.R.C.S.
Herbert Davies, M.D.
August Dupré, Ph.D.
Joseph Fayrer, M.D.
Augustus H. Lane Fox, Colonel.
Francis Stephen Bennet François de Chaumont, M.D.
Alfred Henry Garrod, B.A.
James Geikie, F.R.S.E.
James Whitbread Lee Glaisher, M.A.
Thomas Minchin Goodeve, M.A.
Charles Alexander Gordon, M.D., C.B.
Robert Baldwin Hayward, M.A.
John Baboneau Nickterlien Hennessey, F.R.A.S.
John Hughlings Jackson, M.D.
Emanuel Klein, M.D.
E. Ray Lankester, M.A.