THE PHYSIOLOGICAL ACTION

OF

COCAINE

AND OF ITS

ANALOGUE, BRUCINE.

BY

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[REPRINTED FROM THE THERAPEUTIC GAZETTE, JUNE, 1885.]

DETROIT, MICH.:

GEORGE S. DAVIS, PUBLISHER.

1885.

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QUITE recently I undertook to investigate the physiological action of cocaine, not with a view of adding anything new to its already extensive literature, but chiefly for the purpose of personal familiarization with the physiological behavior of the drug. Its action in many respects was so striking and so different from most other drugs previously investigated, that it seemed to me to stand isolated in the experimental world, as it actually did in the clinical field. Further inquiry, however, showed that there is another agent which behaves very much in the same manner, and which shares the anæsthetic property of cocaine, although probably to a less degree. I have no doubt that further research with the same, or perhaps other and superior methods, will succeed in showing that there are still other drugs which have the power of allaying local sensibility in common with cocaine. The agent alluded to is brucine, an alkaloid contained in the seeds of strychnos nux vomica, and a twin sister of strychnine. To give the data of the investigation in their true order, the necessary points in the action of cocaine bearing on that of brucine will first be given, after which the experimental details of brucine will be presented.

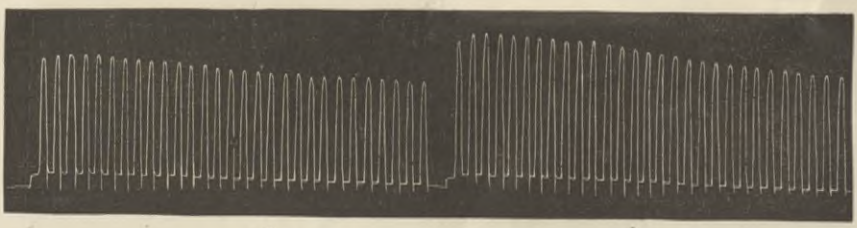
HYDROCHLORATE OF COCAINE.

Action on Frog's Ventricle.—Its action on the isolated ventricle agrees in some and differs in other respects with many of the agents which I had previously investigated.* In its minimum dose, which was ascertained to be 1 to 160,000,—*i.e.*, 1 part of cocaine to 160,000 parts of a two per cent. blood solution,—it gives stronger and more vigorous pulsations than the two per cent. solution of blood alone can give, as is shown by *a* and *b* of Fig. 1.

It also affects the conductivity of the ventricle like ammonia, soda, digitaline, caffeine, morphine, delphinine, etc.,—*i.e.*, in minimum doses it enhances the nervous irritability, and in maximum doses, or in continued minimum doses, the nervous irritability is reduced to zero; but then, unlike the above-named agents, it arrests the heart in diastole, and not in systole, as they do, or cause the heart to become wild and unmanageable, as some of them do, but it gently calms the heart down until it is completely arrested, when, as soon as it is liberated from the influence of poisonous doses, it rebounds and pulsates as before. In Fig. 2 is shown the characteristic arrest of the heart by maximum doses of cocaine (1 to 1000) and by maximum doses of digitaline, the latter being selected as a fair specimen of those agents which cause systolic arrest. The tracing (*a*) given by cocaine maintains a parallel position to the abscissa, while (*b*) that given by digitaline rises far above the abscissa, showing that during the process of arrest the heart is most firmly contracted.

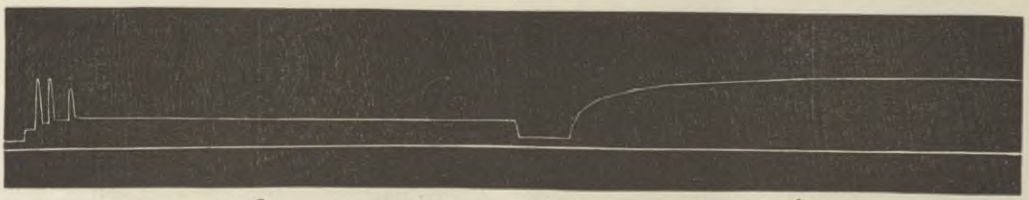
Another characteristic of cocaine is the suddenness with which it depresses the nervous irritability of the heart. In the space of a few minutes the minimum stimulus of the induction apparatus sinks many centimetres, showing that it blunts the impressibility of the heart in a manner similar to that with which it is known to blunt the sensibility of man.

* See my article on the "Action and Antagonism of some Drugs on Frog's Ventricle," THERAPEUTIC GAZETTE, February, 1885.



a. *b.*

Fig. 1.—*a*, tracing given by two per cent. blood solution alone.
b, tracing given by 1 part of cocaine added to 160,000 parts of two per cent. blood solution.



a *b*

Fig. 2.—*a*, tracing of cocaine arrest of the frog's heart.
b, tracing of digitaline arrest of the frog's heart.

General Action on the Frog.—My observations on the general action of cocaine on the frog tally with those of other observers. Subcutaneous introduction of 1.0 ccm. of one-half per cent. solution is followed in a few minutes by general convulsions, and afterwards by general hyperæsthesia. The convulsions are undoubtedly spinal, since they are produced and continued after the medulla is divided. The general action of cocaine does not diminish general sensibility. When smaller doses are given, a stage of motor paralysis precedes that of convulsions. In still smaller doses the convulsions are hardly pronounced, or do not exist at all. Respiration ceases before cardiac action.

In order to make an intelligent comparison between its general action and that of brucine, a few experiments will be detailed here.

Experiment 1.—Made for the purpose of testing the general influence of cocaine on the frog. Frog small, but active. Respiration 56 per minute.

9.35 A.M. Injected 1 ccm. of one-half per cent. solution of cocaine (grain $\frac{1}{13}$) subcutaneously.
9.40 A.M. Respiration 42; jumps on being touched.
9.41 A.M. Left anterior foot stretched to one side.
9.42 A.M. Begins to drag posterior extremities; anterior legs normal.
9.43 A.M. Remains on back and croaks.
9.44 A.M. Respiration 32; moves legs on pinching, and makes unsuccessful efforts to get off back.
9.45 A.M. Lies with outstretched legs.
9.47 A.M. Still has power to raise body with anterior extremities, but posterior extremities are outstretched and motionless.
9.50 A.M. No motion on pinching hind legs, but moves hind legs and whole body when anterior legs are pinched; croaks; becomes convulsed.
10.00 A.M. Posterior extremities are paralyzed; respires only occasionally.
10.02 A.M. Motion only in anterior extremities.
1.10 P.M. Heart arrested in diastole; filled with black blood.

Experiment 2.—To test large doses of cocaine injected subcutaneously. Frog medium size. Respiration 50 per minute.

9.37 A.M. Injected 2 ccm. of one-half per cent. solution of cocaine (⅛ grain) in left back.
9.40 A.M. Spontaneous convulsions.
9.45 A.M. Convulsions continue; respiration spasmodic.
9.50 A.M. Spasms not continuous, but occur at intervals of twenty or thirty seconds.
10.00 A.M. Touching any part of body produces spasm.
10.10 A.M. Lies flat on belly.
11.00 A.M. Lies helpless in any position.
11.30 A.M. Occasional spasms only; respiration ceased.
12.00 M. Division of medulla; spasms continue.
12.15 P.M. Tendency to spasms disappearing.
12.25 P.M. Spasms ceased; completely paralyzed.
12.30 P.M. Heart pulsations, 22.

Local Action on Frog.—At the seat of hypodermic injection or of local application reflex sensibility is always diminished.

Local Action on Man.—The invariable impairment of local sensibility in man is too well known to have attention directed to it here.

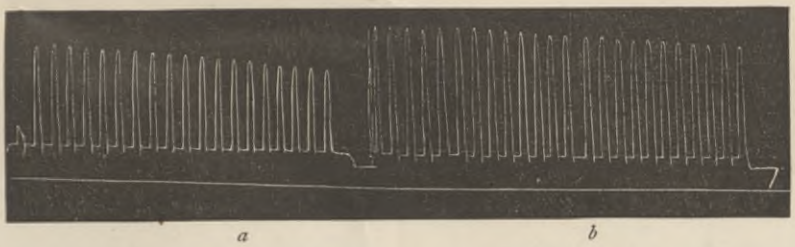


Fig. 3.—*a* represents tracing given by two per cent. solution of blood alone. *b* represents tracing given by 1 part of brucine added to 160,000 parts of two per cent. blood solution.

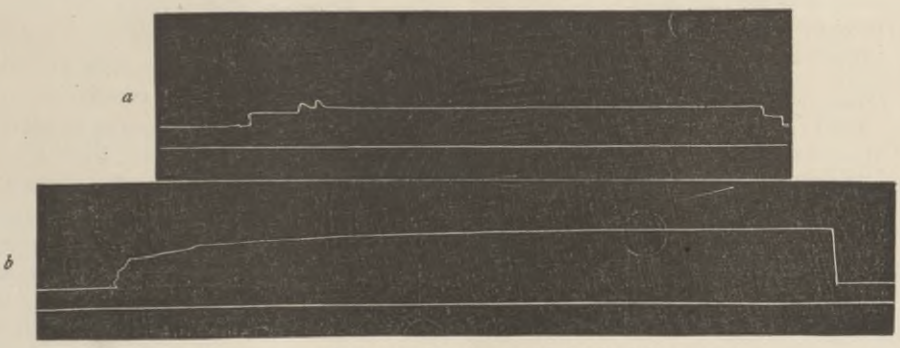


Fig. 4.—*a* indicates the brucine and *b* the digitaline arrest.

BRUCINE.*

The action of this drug was always regarded as being identical in kind to that of strychnine, only differing in degree. When I first tested its action on the frog's ventricle it behaved so similarly to the action of cocaine on the same organ that I ventured to give it a more thorough trial, with a view of ascertaining whether it had any power like cocaine to deaden sensibility. It was soon found, however, that the ordinary preparations in the market were worthless for the purpose sought, since they invariably brought out the strychnine effects soon after the beginning or near the termination of the experiment, no matter how small the quantity used, although in most instances there was some evidence of anæsthesia. After confronting considerable difficulty I succeeded, through the advice of Dr. Squibb, of Brooklyn, in obtaining a very pure specimen of the drug from the Chas. T. White Chemical Company, of New York City, to whom my thanks are due for the kindness and aid which they extended to me throughout this investigation.

Its Action on the Frog's Ventricle.—Its effects in minimum doses of 1 to 160,000—*i.e.*, 1 part of brucine to 160,000 parts of a two per cent. blood solution—were markedly stimulant, as is shown in Fig. 3 : *a* shows the tracing which was given by the two per cent. blood solution alone, while *b* marks the action of 160,000 parts of same blood with one part of brucine superadded.

Nearly all the agents previously investigated which had a special affinity for the conductivity of the heart arrested it in systole, while brucine, contrary to this observation, and in consonance with the action of cocaine, influences conductivity, but arrests the heart in diastole. This is illustrated in Fig. 4, where the brucine arrest is contrasted with that of digitaline. The heart was first arrested with brucine (*a*) and immediately afterwards with digitaline (*b*).

Again, the suddenness with which it depresses the conductivity or blunts the receptivity of the heart is similar to the action of cocaine, as well as its transient disturbing influence on the heart in maximum or in continued minimum doses. These observations led me to believe that its local and general action may be analogous to that of cocaine, and I am able to state that this assumption has been confirmed both by clinical and further physiological research.

* The literature on brucine is very meagre, and I am only able to give the following references :

Prévost : "Action physiologique de la Brucine." C. R. Soc. de Biol., 14 Octobre, 1882. L. Wintzenried : "Recherches experimentales relatives à l'Action physiol. de la Brucine." Diss. Genève, 1882. Brunton : *Amer. Assoc. Jour.*, May 2, 1885, in London letter.

General Action on the Frog.—In my observations on the general action of brucine a number of experiments were made, but only two, which are typical of the rest, will be given here.

Experiment 3.—Made for the purpose of testing the influence of brucine on the frog when subcutaneously injected. Frog small, but active. Respiration 58 per minute.

11.21 A.M. Injected in left back 0.05 ccm. of one per cent. solution of brucine (½ mg. or $\frac{1}{6\,8}$ grain).
11.28 A.M. Respiration 30; frog active.
11.34 A.M. Repeated the same dose in right back.
11.35 A.M. Less active; head inclines to droop.
11.36 A.M. Respiration 28.
11.37 A.M. Croaks, and is slightly paralyzed in posterior extremities.
11.38 A.M. When leg is drawn out allows it to remain in that position for a minute.
11.39 A.M. Left hind leg lies outstretched and paralyzed, but is withdrawn slowly when touched sharply.
11.42 A.M. Respiration 14.
11.43 A.M. Both hind legs lying outstretched and flaccid; the right only withdrawn when touched.
11.44 A.M. Remains on back and croaks.
11.45 A.M. Neither leg moved when touched.
11.47 A.M. Lies flat on belly.
11.52 A.M. Respiration 8.
11.53 A.M. Slight twitches over whole body when legs or webs are touched; hyperæsthesia.
11.55 A.M. Strong blow of breath on body will also call forth a general twitch; respiration ceased.
12.15 P.M. Slight spontaneous momentary spasms.
2.00 P.M. Spasms more pronounced and general.
3.00 P.M. Medulla divided.
3.15 P.M. Spasms still continue.
3.30 P.M. Spasms ceased.
4.00 P.M. Pithed; pulsations of heart 48.

Experiment 4.—Made for the purpose of testing a somewhat larger dose of brucine given subcutaneously. Frog small, and active. Respiration 60 per minute.

4.22 P.M. Injected 0.2 ccm. of one per cent. solution of brucine (2 mg. or $\frac{1}{2\,1}$ gr.) in left back.
4.23 P.M. Symptoms of motor paralysis in posterior extremities.
4.25 P.M. Respiration 54.
4.26 P.M. Decided loss of motion in posterior extremities.
4.27 P.M. Convulsions; legs outstretched and stiff; rolls on back; respiration ceased.
4.30 P.M. Spasm can be induced by touch; general hyperæsthesia.
4.35 P.M. Lies outstretched and flaccid on belly, and a very slight spasm can only be induced by touch; tendency to spasm greatly lessened.
4.45 P.M. Legs twitch when pinched hard; lies flaccid and paralyzed.
4.55 P.M. No response to touch or pinching.
5.55 P.M. Heart arrested in diastole.

These experiments point out that in its general action brucine provokes a short period of at least motor paralysis, which is succeeded by convulsions; that the loss of motion first affects the posterior extremities; that the convulsions are spinal; that there is no marked impairment of general sensibility, but, on the contrary, preceding and during the convulsive stage there is confirmed hyperæsthesia, which is succeeded by complete motor and sensory paralysis; and, finally, that respiration ceases before the heart is arrested.

Local Action on Reflex Frog.—In these experiments the secondary coil of an induction apparatus is joined to a Du Bois key, this is connected with a Pohl's commutator, and from here two wires were joined to each foot by means of a rubber band, thus bringing each foot into a separate electric circuit. In due time, after the brain of the frog was destroyed, the irritability of each leg was tested with single induction shocks, and the minimum stimulus required to call forth reflex motion noted. After which the leg was from time to time immersed in a solution of brucine, or enveloped with blotting-paper saturated with same solution, and the minimum reflex irritability tested at intervals.

Experiment 5.—Reflex frog; medium size; four per cent. solution of brucine employed.

Minimum reflex irritability of	Left Leg.	Right Leg.
8.46 A.M. Before immersion	10.0	9.0
8.56 A.M. Left leg immersed in solution for eight minutes.		
9.00	9.0	9.0
9.03	8.5	9.0
9.06	8.5	9.0
9.09	7.5	9.0
9.12	7.0	9.0
9.15	7.0	9.0
9.18	6.5	9.0
9.21	6.0	9.0
9.24	6.0	9.0
9.27	6.0	9.0
9.30	6.0	9.0
Left leg immersed again for five minutes.		
9.36	5.5	9.0
9.39	4.5	9.0
9.43	4.0	8.5
9.46	3.5	8.0
9.49	3.0	8.0
9.51	3.0	8.0
9.53	2.5	8.0
9.56	2.0	7.5
9.59	1.5	7.5
10.02	1.0	3.5
10.05	0.0	3.5
10.08 No reflex	0.0	0.0

10.09 A.M. No reflex when posterior, but when anterior legs are pinched both hind legs are withdrawn, showing that they still have reflex power when the afferent im-

pulse is carried to the spinal centre through the sensory nerves of the anterior extremities.

10.18 A.M. Reflex action completely paralyzed; no motion on pinching any part of the body; frog lies flaccid and motionless on glass plate.

9.20 A.M. (Next day.) No reflex action; heart's pulsations 18.

12.00 P.M. Heart arrested in diastole; no spasms throughout.

Experiment 6.—Reflex frog; medium size; ten per cent. solution employed by means of saturated blotting-paper.

Minimum reflex irritability of	Left Leg.	Right Leg.
6.09 P.M. Before application of brucine	8.5	8.5
Blotting-paper applied now, and during intervals of observation.		
6.11 P.M.	8.5	8.5
6.13	8.0	8.5
6.15	7.5	8.5
6.17	7.0	8.5
6.19	6.5	8.5
6.21	6.5	8.5
6.23	6.0	8.5
6.25	6.0	8.5
6.27	6.0	8.5
6.29	5.5	8.5
6.31	5.0	8.5
6.33	4.5	8.0
6.35	4.0	8.0
6.37	3.5	8.0
6.39	3.0	8.0
6.41	2.5	8.0
6.43	2.0	8.0
6.45	2.0	8.0
6.47	2.0	8.0
6.49	2.0	8.0
6.51	1.5	8.0
6.53	1.0	8.0
6.55	0.5	8.0
6.57	0.5	8.0
6.59	0.5	7.5
7.01	0.0	7.5
7.03	0.0	7.5
7.05	0.0	7.5
7.07 Partial reflex	0.0	7.5
7.09 " "	0.0	7.0
7.11 " "	0.0	7.0
7.13 " "	0.0	7.0
7.15 " "	0.0	7.0
7.17 No reflex	0.0	7.0
7.21 "	0.0	7.0
7.30 "	0.0	0.0

7.31 P.M. Pinching web of left foot calls forth no response, but on pinching anterior legs both hind legs are drawn up and flexed.

7.33 P.M. Very sensitive in anterior part of the body; both hind legs are stretched out and paralyzed; both are drawn up when anterior extremities are pinched.

8.15 P.M. No reflex motion in posterior extremities when strongly stimulated or pinched, but only slight reflex motion in them when anterior legs are pinched.

8.20 P.M. Electric stimulus, which is not able to call forth any motion when applied to posterior extremities, will cause contraction in them when applied in same strength to anterior extremities; no spasm or convulsion throughout the whole experiment, although the brucine was certainly absorbed during the experiment.

These experiments prove without a doubt that reflex action is disturbed not by virtue of motor, but of sensory paralysis, when brucine is locally applied; that it not only produces sensory paralysis in the leg to which it is applied, but by gradual absorption through the skin it also affects the sensibility of the opposite leg, and, finally, that of the whole body; and that paralysis of motion follows that of sensation.

Other experiments, the details of which it is not necessary to give here, also showed that the local application of five per cent. solution to skin of frog in other parts of the body diminished sensibility.

Local Action on Man.—The benumbing action of brucine on the mucous membrane in health is not so prompt as that of cocaine in the same strength. I cannot account for this unless the former is more rapidly absorbed and diffused than the latter. A ten per cent. solution will relieve the scalding on the tongue caused by the application of Cayenne pepper; and a five per cent. solution acts very readily in aphthæ of the mouth, applied with a camel's-hair brush. The same solution also cured a toothache in an old stump in a very few minutes.

It is, however, on the cutaneous surface where its action is the most decided and definite. On the back of the hand even the weaker solutions produce a benumbing effect, while a ten or a twenty per cent. solution causes a very marked impairment of sensibility. This is best demonstrated if it is applied to a hairy part of the hand or arm, and allowed to remain for ten or fifteen minutes, and then the sensibility of the spot compared with that of a neighboring one by pulling the hair. Applied croton oil liniment to arm, and in the course of six hours two applications of a five per cent. solution of brucine to the part affected relieved the itching shortly, and the pustulation also seemed to disappear from that time on. The same solution applied to an intense superficial cutaneous pain, caused by a too lengthy application of a mustard-plaster, brought immediate ease to the patient. I applied a five per cent. solution in two cases of pronounced cutaneous pruritus,—which was in all probability a re-

flected condition dependent on some uterine irritation,—with marked relief in both of them. The two cases were nearly identical, and hence I will only detail one, as follows:

May 13, 1885.—Mrs. H., aged 36, has been suffering with a violent itching of the skin, only during the night, for the last year and a half. It is worst just before menstruation. It began in the groins and loins, then extended down both lower limbs, and finally up to her head. She says the itching is terrible, and comes on every night about bedtime, and often keeps her awake nearly a whole night; and so she gets up in the morning as tired as she was when she lay down.

Treatment.—Ordered a five per cent. solution of brucine to be brushed over the affected parts on going to bed, and to be repeated every half-hour until relief is afforded.

May 15.—She reports to-day that she applied the brucine for the last two nights,—the first night three times, and the second night only once,—and it relieved the itching entirely. She says she had not slept so well for a long time as she did the last two nights.

May 19.—She reports that one application on going to bed sufficiently allays all itching for that night.

May 21.—Still improving.

General Remarks.—To obtain the full anæsthetic property of brucine it is important to possess a pure article, and it is needless to point out that almost all the commercial specimens of the drug contain a large percentage of strychnine, and are therefore worthless, and may be even dangerous for this purpose. I do not wish to maintain that absolutely pure brucine, even if it can be obtained in this state, is entirely harmless, especially since some chemists hold that it is very difficult, if not impossible, to get brucine entirely free from strychnine; but I am convinced that there is a marked difference in the purity of the various preparations which I used, and that the one which gave the best results brought out the anæsthetic property of brucine in direct proportion to the absence of the strychnine or convulsive effects.

My opportunity for testing its clinical value has been limited to the above detailed observations, but it will probably prove to be a valuable agent in the treatment of irritable and superficial affections of the skin, and, perhaps, also of the mucous membranes. Of this last I would speak guardedly, for it seems to act more promptly on the outer than on the inner coverings of the body.

It is very readily applied with a small sponge or camel's-hair brush, and from ten to fifteen drops can be employed at a time, and even more if the affected spot is extensive. If the weaker solutions are inefficient the stronger ones can be used. It shows its effects in from five to ten minutes. In making a solution of the alkaloid five drops of hydrochloric or of sulphuric acid must be added to each gramme. It is preferable to use either the nitrate or the sulphate of the alkaloid.

151 N. Fifteenth St., May 21, 1885.