REICHERT (E.T.)

A COMPARATIVE STUDY OF THE PHYSIOLOGICAL ACTIONS OF BRUCINE AND STRYCHNINE.

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BUT little experimental and clinical investigation has been made with brucine, its more potent and cheaper sister-alkaloid, strychnine, having overshadowed it. However, what records we do possess indicate, for the most part, that these substances exert essentially the same influences upon the organism, the differences being in degree rather than in kind. One serious difficulty met in the studies of the actions of brucine has been that the preparations commonly found in the market are, to a greater or less extent, contaminated with strychnine, usually to such a degree that whatever actions might have been exerted by brucine seemed entirely superseded by the more powerful influences of the strychnine. Thus, in the elaborate experimental study of brucine made by Wintzenried (*Inaug. Dissertation*, Geneva, 1882) the results so closely resembled those caused by strychnine that it is still believed by many leading pharmacologists that the phenomena were due to the contaminating strychnine.

There are, however, on record certain statements which lead to the belief that brucine does possess

physiologic properties entirely distinct from those of strychnine. Thus, Mays, in observations on frogs and man (*Therapeutic Gazette*, June, 1885), found that pure brucine acts as a strong local anesthetic, and Robins (*Philadelphia Medical Times*, 1879, p. 228) also noted that this substance depresses the sensory nerves. Mays asserts that brucine induces in the frog a short period of motor weakness, or even paralysis, in the posterior extremities preceding the period of convulsions. There is also evidence to indicate that brucine is of the nature of a motor paralyzant (Klapp, *Journ. Nerv. and Ment. Disease*, 1878, p. 619; Wintzenried, *loc. cit.;* Robins, *loc. cit.*). Finally, Brunton states (*Journ. Chem. Society*, 1885, p. 143) that brucine is innocuous when taken by the stomach.

While we thus have reasons for the belief that there are important dissimilarities in the physiologic actions of these two alkaloids, it is not possible in the light of present knowledge to say to what extent they are due to variations in the purity of the drug used, to dosage, to the differences in the species of animals employed, etc.

The object of the present inquiry has been to determine to what degree important physiologic actions of brucine and strychnine are related. To that end essentially the same line of investigation was carried out as in my recent elaborate research with strychnine (*Therapeutic Gazette*, March, April, May, and June, 1892), which will form the basis of comparison with the results of the present investigation. Over 100 experiments were made, about one-fourth being upon dogs, and the re-

mainder upon frogs. The brucine was made by Merck, a standard preparation, guaranteed to be *absolutely free from strychnine.* The specimen was subjected in our laboratory to the most rigid testing, and the results fully substantiate Merck's claim.

In the frog, after *minimal* lethal doses, no marked differences are observed in the results caused by brucine or strychnine, other than that the former is less prompt in action, that the motor disturbances caused by it are of less violence, and that it affects the volitional centers sooner and more powerfully. In the brucinized frog a failure of voluntary motion and an increase of reflex excitability are simultaneously developed, the former progressing usually with greater rapidity than the latter, so that volitional movement is, as a rule, lost before the exaltation of reflexes is sufficient to provoke convulsions. This loss of voluntary motion may be mistaken, as by Mays, for a general condition of motor paralysis. In the strychninized frog voluntary motion is also lost, but never until after the onset of convulsions. The differences, therefore, are not in kind, but in degree ; brucine acting with less vigor as a convulsant, and with greater power upon the cerebrum. After the administration of much larger doses absolutely no differences are detected in the phenomena exhibited by the two sets of frogs. Brucine being absorbed with less readiness than strychnine is consequently less prompt in its effects.

The belief of Robins and Mays that brucine depresses the sensory nerves, leading to the conclusion that this action is unlike any of strychnine, is true in fact, but not in deduction. Neither exerts any

influence on the sensory nerves in minimal lethal doses, but both depress and finally paralyze these nerves when the poisons are given in great excess.

In the mammal, as in the frog, the only important differences in the phenomena noted are those of degree, and not of kind.

The statement made by Brunton (*loc. cit.*) that brucine is innocuous when administered by the stomach is not supported by sufficient evidence to give it any value, and, besides, is contradicted by the results of my own experiments. Brunton's conclusion is based upon the result of a single and by no means satisfactory experiment made upon a rat, to which he gave 0.1 gram of pure brucine, mixed with suet, so that the animal ate it readily. The rat was not affected by the dose, although another, to which the same quantity was administered by injection into the abdominal cavity, fell into convulsions within three minutes and died.

The records of one of my experiments will be sufficient to prove that absorption does take place through the stomach, but with much less rapidity than in the case of strychnine:

EXPERIMENT.—Dog; weight, 8617 kilos. 9.30. Gave per stomach through a catheter, 0.18 gram of brucine. 9.40. Acts as though he heard flies flying about his head; otherwise no apparent change. 10.30. An occasional twitch or jerk of the skin, or in one of the legs. 10.35. Twitchings and jerkings more pronounced and observed in the skin, ears, head, and extremities; reflex activity greatly increased, a slight touch causing considerable muscular disturbance; there is pronounced muscular stiffness, especially when any movement is attempted; respiration

is very quiet and 24 per minute. 11.40. Vomits; respiration increased in frequency; and panting. 11.55. Salivation; marked rigidity; great hyperesthesia; a breath of air induces a condition of rigidity bordering on tetanus. 11.57. Tetanus, followed by slow, deep respirations, which gradually pass to those of a frequent and panting character. 12.20. Quiet and sickly; respirations, 140; profuse salivation; occasional slight spasms of the body and legs. 12.26. Opisthotonos; failure of respiration; heart continued beating for several minutes after the cessation of respiration.

The non-toxic result of Brunton's experiment is doubtless to be attributed to the extremely slow absorption of the poison, owing to its admixture with suet.

Whatever dissimilarities may exist in the actions of brucine and strychnine are best elicited by general and special studies, such as were pursued in the investigations with strychnine already alluded to.

When a 1 per cent. solution of brucine is injected into the external jugular vein of a dog, the general results which follow are not apparently in any way distinguishable from those resulting from the injection of strychnine. There occurs within a few moments a condition of muscular excitement, which rapidly passes into one of violent tetanic convulsions, and death ensues immediately from an arrest of respiration, or, after a time, from exhaustion. Should, however, forced artificial respiration be practised at and after the time of the convulsive seizures, the spasms gradually disappear, the general condition of the animal becomes in most respects the same as just before the convulsions, and the

effects of the poison slowly wear away. But if with the appearance of the convulsions the injection of brucine or strychnine is continued, the tetanus grows less and less violent, voluntary motion is lost, reflex excitability rapidly disappears, the spasms give place to somewhat rhythmical jerkings of the muscles (choreic in character), and these to twitchings, which, in turn, are lost, and the animal lies absolutely motionless, save for the movements due to artificial respiration and the heart-beats. The circulation and heat processes, and other important functions, generally remain in good condition, and the dog may be kept alive for hours, if not days, thus paralyzed, if brucine or strychnine be from time to time injected.

The state of absolute muscular quiet is not, as a rule, of long duration, unless the dose has been unnecessarily large, for usually, in the course of fifteen or twenty minutes, fibrillary twitchings reappear, invariably in the inverse order of their disappearance from the various parts. These movements become more and more marked, gradually passing to violent rhythmical jerkings, and finally to clonic convulsions.

These remarkable changes from the normal state to violent tetanus, and finally to complete motor paralysis, occur with such rapidity that the latter stage may be reached within three minutes.

The quantity of brucine, when intra-venously injected, necessary to cause death, is about 0.008 gram to the kilo of body-weight; and of strychnine about 0.0002 gram. The dose required to produce absolute motor quiet is for both poisons about

the same, being from 0.015 to 0.020 gram per kilo of body-weight; strychnine being, perhaps, a little more powerful. Thus, it will be observed that while strychnine is greatly more powerful as a convulsant, it is as a paralyzant of practically the same toxicity as brucine.

The relative toxicity of strychnine, compared with that of brucine, is, according to Magendie, 12:1, and according to Andral 24:1, and according to my experiments about 40:1 for the dog and about 50:1 for the frog. The differences given in the proportions of Magendie, Andral, and myself, respectively, are doubtless owing largely, if not solely, to the degree of purity of the brucine employed.

These figures by no means indicate, as before stated, the relative potencies of the two poisons upon different parts of the organism. As is well known, both substances cause death by asphyxia, which results from the violent convulsive seizures; but, as I have pointed out in my memoir on strychnine, the virulence of strychnine as a convulsant in relation to its other powers is so extraordinary that a fatal result ensues long before many other important actions are developed. It is only by the prevention of the continuance of the convulsive seizures, the use of artificial respiration, and the administration of comparatively enormous doses of the drug, that its full train of action is obtained. This statement holds good for brucine; consequently, the figures indicating that strychnine is so many times more powerful than brucine signify that it is that many times more potent as a convulsant; and they must not be taken as an expression of the rela-

tive intensities of the actions of the drugs on the various parts of the economy. In some respects brucine is of equal toxic value in its action; in other respects, of greater value; and in still other respects, of less value.

A careful comparison of the results of the detailed studies made with these alkaloids shows so few and unimportant differences that the conclusions arrived at from the study of strychnine are applicable to brucine, with slight additions and modifications. In the following summary where differences exist they are distinctly stated; otherwise it may be considered that the actions and effects are identical.

1. The minimum lethal dose of brucine for the dog, when intra-venously injected, is about 0.008 gram to the kilo of body-weight, and of strychnine about 0.0002 gram, the relation being 1:40. In the frog the minimum lethal dose of brucine is about 0.1 gram, and of strychnine about 0.002 to the kilo of body-weight, when subcutaneously injected.

2. Doses of from 0.015 to 0.020 gram to the kilo intra-venously injected cause a condition of absolute muscular quiet, and by means of artificial respiration the animal may be kept alive in excellent general condition.

3. Quantities in excess of 0.1 gram to the kilo may be intra-venously injected in divided doses without causing death, provided that artificial respiration be employed.

4. The toxic actions of brucine and strychnine are so directed to the motor center in the spinal cord that the minimum fatal dose is exceedingly

small, owing to the production of asphyxia or to exhaustion by the violence and persistence of the tetanic seizures. Should artificial respiration be maintained, about 500 times the minimal lethal dose may be injected without an immediately fatal result.

5. By a proper regulation of the size of the dose and the method of administration, the stage of excitement may be prolonged over an almost indefinite period, or may be so brief as to last for but a few seconds.

6. During the *stage of excitement* the following actions and effects are observed:

a. The motor disturbances and convulsions are of spinal origin.

b. The sensory nerves and muscles are unaffected.

c. The motor nerves, after the onset and continuance of convulsions, become depressed from overwork.

d. The pulse-rate is first lessened in frequency, then increased, and finally diminished. The first effect is due to a stimulation of the cardio-inhibitory apparatus, the second to its depression, and the last to a depression of the excito-motor ganglion, or automatic-motor ganglion in the heart.

e. The arterial pressure is primarily diminished, then greatly increased, and at last diminished. The first effect is due to some obscure action on the vasomotor centers in the medulla oblongata; the rise of pressure to a stimulation of the vaso-constrictor centers in the same part; and the final fall, to a depression of the heart and vasomotor centers. In curarized animals the rise of pressure due to stimu-

lation of the vasomotor centers is relatively and absolutely greater than in the non-curarized animal.

f. The respiration-rate is not specifically affected, unless it be in the nature of a decrease, or during the period of convulsions, when it may be decidedly increased.

g. The bodily temperature is increased.

7. During the *stage of paralysis* the following are noted:

a. The muscles are not in the least affected unless after enormously excessive doses.

b. The sensory nerves are inexcitable to strong electric currents.

c. When the motor nerves are subjected to a powerful faradic current, spasm of the muscles supplied no longer occurs, although the nerves transmit impulses from the nerve-centers—irritability is lost, but conductivity remains.

d. The pulse-rate is reduced, but the height of the curves is increased; the first effect being due to a depression of the motor ganglia in the heart, and the second effect to the greater filling of the viscus with blood, and perhaps to a direct stimulation of the heart. The cardio-inhibitory fibers are paralyzed, but no increase in the frequency of the pulse-rate is observed, owing to the predominance of the depressant action on the heart-ganglia. Stimulation of the vagi causes smaller pulse-curves, and a slight increase in the frequency of the beats.

e. The arterial pressure is increased, unless the dose has been greatly in excess, when it is diminished. The increase is due to a stimulation of the

vasomotor centers in the medulla oblongata, and the decrease to a depression of the heart and to vasomotor paralysis. The increase of pressure is greater and more persistent in curarized animals. In non-curarized animals the pressure sinks below the normal immediately after the tetanic paroxysms, but in those curarized this depression is less marked. Asphyxia and electric stimulation of a sensory nerve fail to cause a rise of pressure, as in the normal animal; on the other hand, asphyxia is always accompanied by a fall.

f. The hemoglobin is in some way affected so that it cannot be oxygenated to the normal degree, although the spectroscope reveals nothing but oxyhemoglobin.*

g. The temperature may be increased or decreased by brucine, but is always increased by strychnine. Cocaine is unable to cause its characteristic increase of heat-production and temperature, as in the normal animal. Apparently, both strychnine and brucine paralyze the accelerator thermogenetic centers, and leave intact the automatic thermogenetic centers.

h. The paralytic condition caused by strychnine and brucine closely resembles that produced by curare, but is in many ways entirely distinct.

8. The *chief differences in the physiologic properties of brucine and strychnine* are as follows:

a. Brucine is less rapidly absorbed than strychnine, and, as a consequence, is less prompt in its actions.

b. Brucine is from forty to fifty times less powerful as a convulsant, and, therefore, proportionately less fatal.

c. Brucine acts relatively more powerfully on the volitional centers in the frog than as a motor excitant, with the effect oftentimes of causing in these animals a loss of volitional movement preceding the stage of convulsions. In mammals, however, it does not seem that either poison ever destroys volition before the appearance of convulsions.

d. In excessive doses brucine is more poisonous to the sensory nerves than is strychnine.

e. During the last stage of the poisoning the action of brucine on bodily temperature is uncertain, while that of strychnine is positive. Brucine is, ultimately, a stronger depressant to the heart, and after enormous doses more toxic to the muscles.

9. The green frog (*Rana esculenta*) is somewhat more susceptible to brucine than the spotted frog (*Rana temporaria*). The same difference I have noted with strychnine.

The results of this research render it obvious that the physiologic actions of brucine and strychnine are essentially identical, the differences being practically solely in degree, and not in kind. This, together with the fact that the convulsant action of brucine is in the mammal about forty times less than that of strychnine, indicates that brucine will prove not only a safer drug, but of infinitely greater value as a general therapeutic agent.

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