A STUDY OF RESPIRATION AND CIRCULATION IN PICROTOXIN CONVULSIONS

THE POSSIBLE BEARING OF THIS STUDY ON THE THEORIES OF PATHO-
GENESIS OF EPILEPTIC CONVULSIONS *

LEWIS J. POLLOCK, M.D., AND WILLIAM H. HOLMES, M.D.
CHICAGO

The convulsion is the most prominent symptom of epilepsy. It is this symptom which has lent itself most extensively to the study of the pathogenesis of this disorder. There are many phenomena associated with convulsions which have received but scant attention. Chief among these are the circulatory and respiratory disturbances.

In *A Study of Respiration and Circulation in Epilepsy*¹ one of us found that preceding the convulsion in a case of *petit mal*, admirably suited for continuous respiratory and circulatory tracings, a constant series of events occurred (Fig. 1).

A preliminary rise in blood pressure was noticed twenty-six to sixty seconds before the convulsion; when the rise took place over thirty seconds before a convulsion the blood pressure usually fell again slightly. Immediately preceding the convulsion by from nine to twelve seconds there was a sudden marked drop in blood pressure, which remained relatively low during the time occupied by the *petit mal* attacks.

Two seconds later the aura occurred. A period of apnea which preceded the convulsion or its equivalent then followed in from four to nine seconds.

From the facts that respiratory and circulatory disturbances preceded the convulsion or equivalents, the conclusion was reached, that in some cases of *petit mal*, the site of discharge is in the medulla and pons, and furthermore that the medulla and pons participate in the discharge in all cases of epilepsy whether this discharge originates there or not.

If convulsions which are caused by a discharge in the medulla and pons are accompanied by a train of circulatory and respiratory symptoms, it would seem likely that these symptoms should be present in a convulsion artificially produced by a medullary convulsant.

* Submitted for publication April 21, 1915.

* Read before the Chicago Neurological Society, March 18, 1915.

* From the Departments of Neurology and Pathology, Northwestern University Medical School.

1. Pollock, Lewis J., and Treadway, W. L.: A Study of Respiration and Circulation in Epilepsy, THE ARCHIVES INT. MED., 1913, xii, 445.

In this paper we wish to describe the circulatory and respiratory changes accompanying the convulsions produced by the administration of picrotoxin.

Picrotoxin is the active principle of *Cocculus Indicus*, or fish berry. It is a medullary convulsant (Roeber²). The data tending to uphold this contention will be reviewed briefly below.

Its action along with coriamyrtin, is analogous to toxiresin and digitaliresin (Perrier³).

The description of the action of picrotoxin, will be limited to the convulsions, and its effects on the autonomic nervous system.

The convulsion resulting from the administration of picrotoxin has been recognized as being very similar to that observed in epilepsy, by many workers. It will be but briefly described. You may refer to a classical description by J. Crichton Browne.⁴

Following an injection of picrotoxin in a dose sufficient to produce convulsions without causing death (2 c.c. of 4 per cent. alcoholic solution), the animal after a period of time, in which vomiting and sialorrhea may be noted, becomes quiet; sits in one place, and does not respond to calls. Then follows a period of unrest and apparent apprehension. The animal begins to tremble in fore or hind legs, or both, and lies on his side, at times trying to stand erect. Light twitches of face and neck muscles occur becoming stronger and stronger; the head is drawn backwards on the neck. Then immediately there follows a generalized clonic convulsion with clonic champing of the jaws, closing of the eyelids, marked frothing at the mouth, and involuntary urination. During the convulsion the pupils are dilated. The clonic convulsive movements imperceptibly change to running movements of the fore and hind legs, become slower and slower, and finally cease. The animal now remains quiet, lying on his side, and after some effort regains the erect position. After a period of time, varying with the size of the dose, another convulsion occurs.

It is generally admitted by pharmacologists that picrotoxin is a medullary convulsant. Adverse contentions, however (Bechterew,⁵ Browne⁴), have not been replied to adequately.

In the pharmacologic sense, convulsions are not clearly defined. They include many spasmodic movements, tremors, twitchings, and tetanic contractions. The pharmacologists have ignored, to a great extent, the work of other departments in pathologic physiology in the

2. Roeber: Physiologische Wirkungen des Pikrotoxins, Arch. f. Anat. u. Physiol., 1869, p. 38.

3. Perrier: Toxiresin, etc., Arch. f. exper. Path. u. Pharmacol., 1875, iv.

4. Browne, J. Crichton: Brit. Med. Jour., 1875.

5. Bechterew: Functionen der Nervencentra, 1908, vi, 187.

study of convulsions. The difficulty in correlating pharmacologic data with that obtained by neurologists and physiologists can therefore readily be seen.

On the other hand, the neurologists who have attempted to prove that the medulla and pons are not directly concerned in convulsions, have not taken pharmacologic data into consideration. The results of both must be considered in reaching a correct conclusion.

Roeber² and Grünwald,⁶ working with picrotoxin, Albertoni⁷ with cinchonidin and camphor, and Perrier³ with toxiresin, digitaliresin, picrotoxin and coriamyrtin, are the principal workers who have attempted to prove that these various agents are medullary convulsants.

Roeber was able to obtain convulsions with picrotoxin after removal of the cerebrum above the medulla. He contended that picrotoxin is a medullary convulsant.

Since the experiments of Perrier are very clearly given we will review those tending to show that the group of toxins above mentioned are medullary convulsants.

From the fact that these substances cause convulsions he concluded that they act on the central nervous system. On what part of the nervous system they act his further experiments show. After removal of the hemispheres above the optic thalami in frogs, convulsions occur following the administration of the poison. After destruction of the thalami and removal of the hemispheres, convulsions still occur. When the medulla is separated from the spinal cord but two twitches of the head muscles occurred. The rest of the body remained at rest. After cutting through the spinal cord above the lumbar region convulsions occurred in the fore part of the animal only. After section of the right ischiatic nerve the right leg did not participate in the otherwise general convulsion. After the destruction of the medulla the animal quickly became comatose with no convulsion whatever.

He therefore concludes that these substances in causing convulsions act on the central nervous system situated in the medulla oblongata.

J. Crichton Browne⁴ in a purely theoretic manner combats this idea as follows:

Because the thumb and index finger may be moved by galvanic stimulation of the median nerve we do not argue that the movements of these parts are not ordinarily controlled by volition, and so because clonic spasms may occur in rabbits by irritation of the medulla after all other parts above the center have been cut off from it, we cannot argue that such clonic spasms may not proceed from the cerebrum when it remains intact.

6. Grünwald: Zur Kenntnis des Pikrotoxins, etc., *Arch. f. exper. Path. u. Pharmacol.*, 1909, ix, 249.

7. Albertoni: *Arch. f. exper. Path. u. Pharmacol.*, 1882, xv, 258.

It seems to us that Browne's objection is not applicable at all, for if, in experimental animals, the medulla after stimulation by picrotoxin acted only as a collection of fibers whose function is the conduction of impulses, then similar results would be obtained after section below the medulla, for these same fibers are found in the spinal cord. By this very objection Browne admits that the medulla at least shares with the cerebrum and ganglia a peculiar ability to be stimulated by picrotoxin which is not possessed by the spinal cord. If the medulla alone after stimulation by a drug causes convulsions in no wise different from those which are caused by stimulation of the cerebrum and medulla it is reasonable to assume that the convulsions may originate in the medulla. We must, however, admit that it is experimentally impossible to disprove entirely Browne's theoretic objection because it would necessitate the removal of the medulla and the substitution of some tracts leading from the cerebrum to the cord.

Bechterew⁵ has asserted that in his laboratory, after the removal of the hemispheres, clonic convulsions are not caused by the administration of cinchonidin and absinthe, while tonic convulsions occur.

Albertoni⁷ in the most careful work recorded found that in dogs after full operative recovery from half section below the optic thalami with ensuing hemiplegia, cinchonidin produced a generalized bilateral convulsion. He further found that after full operative recovery from ablation of the motor cortex, similar generalized convulsions result from the administration of cinchonidin. He states that under these circumstances the convulsions are slightly diminished when camphor is the drug employed.

Grünwald⁶ observed typical picrotoxin convulsions in a decerebrated cat and dog.

We have found in two experiments on dogs, to be more fully described later, that in one after a section below the optic thalami with a cautery knife and in the other after removal of the cerebral hemispheres and optic thalami, picrotoxin caused convulsions differing in no wise from those occurring in animals with an intact central nervous system.

We are therefore convinced that there are drugs which are medullary convulsants and that picrotoxin is one of them.

In a work, the significance of which we will emphasize later, Grünwald⁶ studied the action of picrotoxin on the autonomic nervous system. He remarked that a review of the literature shows that aside from the production of convulsions and injury to the heart muscle, picrotoxin causes contraction of the pupils (Falck, Roeber, Luchsinger, Perrier, quoted by Grünwald), salivation (Falck, Roeber, Luchsinger, Gottlieb, also quoted by Grünwald), slow pulse (Roeber, Per-

rier, Gottlieb), urinary bladder contraction (Falck, Gottlieb), and erections (Luchsinger). All these disturbances may be attributed to the autonomic nervous system. In his experiments he verified these findings and demonstrated the central action of this poison as follows: After cutting the bladder nerves "no contractions occurred from the administration of picrotoxin."

In a decerebrated cat, poisoned with picrotoxin and showing a vagus pulse, salivation and bladder contractions, these three respective symptoms disappeared on section of the vagus, chorda and pelvic nerves; furthermore these symptoms did not again manifest themselves following a second dose of picrotoxin. After section of the right chorda, and the administration of picrotoxin, there was profuse secretion from the left salivary duct but none from the right. From these experiments he concluded that picrotoxin is a poison acting on the central autonomic nervous system.

We shall now revert to our supposition, that, if the respiratory and circulatory changes associated with a *petit mal* attack are due to a discharge in the medulla then we should find similar respiratory and circulatory changes associated with picrotoxin convulsions.

We shall not burden this paper with lengthy protocols. The experiments were conducted on dogs approximately of the same weight. Ether anesthesia through a tracheotomy tube was employed. The blood pressure was registered by means of a cannula inserted into the carotid artery and connected with a mercury manometer. The respiration was registered from the tracheotomy tube with a Marey tambour attachment. The time of injection of the drug and the beginning of the convulsions was recorded by means of a Du Bois Raymond key and electromagnet. A metronome time marker was employed. The records were made upon a Stoelting kymograph. The picrotoxin was administered as a 4 per cent. solution either intravenously or subcutaneously. The action of the drug is much more rapid and severe when injected intravenously. Of a large number of records of convulsions observed in nine animals, twenty-three have been selected as suitable for study.

The data may be divided into general changes in blood pressure and respiration and the changes associated with convulsions. The general changes will be briefly dealt with. The blood pressure is raised after the administration of picrotoxin. Contrary to the findings of Grünwald we found that in a decerebrated animal the blood pressure did show a rise. A vagus pulse was observed in all cases. Picrotoxin acts as a respiratory stimulant.

With reference to the changes in blood pressure and respiration associated with convulsions, the material may be divided into four groups.

A. Twelve convulsions in three animals following moderate doses of picrotoxin.

B. Two severe convulsions in two animals following large intravenous doses of picrotoxin.

C. Seven moderate convulsions occurring in one animal following a very severe convulsion as the result of a large intravenous dose of picrotoxin.

D. One convulsion in a decerebrated animal.

In Group *A* which we term the typical reaction, we found that the convulsion started with twitching of the muscles, and respiratory irregularity, that preceding these symptoms by from three to ten, usually three to eight seconds, there was a fall in blood pressure which lasted until apnea had occurred. Apnea was concomitant with the severe clonic convulsion and did not precede it.

When respiration continued but was irregular during the convulsion, the blood pressure fell before the convulsion, and commenced to rise about five respirations after the severe clonic convulsion with its accompanying irregular respirations commenced.

In one tracing of Group *B* it was found that the blood pressure rose slightly with the convulsion and was associated with a few muscular twitchings and irregular respirations. A drop in the blood pressure and more marked twitching then occurred, followed by a period of apnea and severe clonic convulsions. The blood pressure continued to fall until almost the end of the period of apnea and then rose again.

In the other tracing of this group no period of apnea was present, and the blood pressure commenced to rise very shortly after the severe clonic convulsions began, having fallen before the convulsion began. It is to be noted that the first tracing of Group *B* is from the same animal that gave the seven tracings in Group *C*.

In Group *C* blood pressure began to fall during the period of apnea and rose during the period of respiration. The convulsion preceded the drop in blood pressure (Fig. 3).

In Group *D* a decerebrated dog, after an injection of picrotoxin developed tetanic convulsive movements, then irregular clonic convulsive movements, and, after a period of quietude a typical tonic-clonic picrotoxin convulsion which ended in running movements. Concomitant with this convulsion there occurred a drop in blood pressure and an increase in the respirations which had been very slow and irregular following the decerebration.

There were no Traube-Hering waves present in any of the tracings. The pulse was slightly increased in rapidity during all convulsions except such as occurred tumultuously where a vagus pulse persisted.

Fig. 1.—1, drop in blood pressure; 2, beginning of apnea; 3, convulsion.

Fig. 2.—Convulsion preceded by drop in blood pressure.

Fig. 3.—Convulsion followed by a period of apnea, during which the blood pressure fell.

From the above facts it may be deduced that the period of apnea does not bear any definite time relation to the drop in blood pressure. In one series the blood pressure began to fall, and in another to rise at the beginning of apnea. When apnea was replaced by shallow irregular respirations the blood pressure showed the same change. We also observed that the degree of blood pressure change is not influenced by the length of apnea, or the degree of respiratory irregularity. The period of apnea when present usually begins with the severe clonic convulsion. The changes in blood pressure, while concomitant with the convulsion, bear no definite time relation to it, neither can they be said to be the cause of the convulsion.

There now remains the interesting observation above noted, that in one series of convulsions the blood pressure rose with the beginning of apnea and fell in another series. In the first the blood pressure fell before the convulsion, in the other the convulsion preceded or was synchronous with the fall. This disparity affords an opportunity for certain definite conclusions. There are but few possible explanations of the cause of the diversity of changes in the blood pressure. The periodic rise and fall of blood pressure may be independent of either the respiratory changes or convulsions. In one series the blood pressure changes are those which regularly precede and accompany the convulsions. In the other series for some reason the blood pressure change may be due only to the period of apnea which results in such a fall of blood pressure as is found in the beginning of the so-called convulsions caused by strychnin, or the fall may be dependent on some change consequent to the convulsion.

In any event one conclusion can be reached. The periodic change in blood pressure is not due alone to either the convulsion or the period of apnea. It occurs in most cases as part of the manifestation of picrotoxin poisoning, and although bearing no time or causal relation to the convulsion, nevertheless occurs about the same time.

The period of apnea can not be so easily explained. It might be the result of the participation of the respiratory muscles in the generalized convulsion. It might be due to the cerebral anemia resulting from the discrepancy of balance between a relatively low general blood pressure and a high intracranial tension (Cushing, Eyster, Pollock). Or it may be due to acapnea, or depression of the respiratory center. Further work must be done to determine the cause.

We must here allude to the statement of Grünwald that the respiratory embarrassment is responsible for the rise in blood pressure in picrotoxin poisoning. While it is true that by the use of artificial respiration he was able to prevent the rise it is true only with regard to the general blood pressure and it is not referable to the changes

about a convulsion. It is remarkable that although the blood pressure changes have been studied extensively in many toxic states, that even in strychnin convulsions the separate phases of blood pressure change associated with a convulsion are not described.

It is generally stated that during a strychnin convulsion blood pressure rises, yet although it does so, suddenly, with the first hard tetanic contraction it drops during the entire period of tetanic apnea and then rises to a great height. This same inaccuracy of observation we have already pointed out in our work on the circulatory and respiratory changes in epilepsy.

It may finally be said that although apnea and definite blood pressure changes occur along with the convulsion caused by picrotoxin, they do not bear the same constant relation to the convulsion as is found in *petit mal* states in man. Yet the independent variation in blood pressure occurring about the time of a convulsion is another proof of the medullary action of picrotoxin, which conclusion has been heretofore supported by its causing medullary convulsions and its action on the central autonomic system. The convulsion of idiopathic epilepsy is made up of a train of symptoms, the motor movements being but one of these.

Respiratory and circulatory changes, salivation, often involuntary urination, at times defecation and perhaps pupillary and thermic changes are as much a part of an idiopathic epileptic convulsion as are the motor disturbances.

Although artificially produced cortical fits may simulate imperfectly some of the motor disturbances of an idiopathic epileptic convulsion, it is only when an "after" generalized convulsion ensues as the result of a long continued cortical irritation, that the remaining symptoms such as salivation, etc., are present. The theory of the cortical origin of idiopathic epileptic convulsions fails, as pointed out by Hirt, to explain the presence of salivation, involuntary urination and respiratory change.

It would seem rather far fetched to search in the cerebral cortex for a center for the origin of these disturbances to place them alongside of Unverricht's area for the production of cessation of respiration and vascular change.

These symptoms may all be attributed to a disturbance of the central autonomic nervous system. They have been observed in picrotoxin poisoning and experimentally proved to be due to the action of this drug on the autonomic nervous system.

Toxic doses of picrotoxin cause not only convulsive motor disturbances but also such other symptoms as salivation, involuntary urination, etc., as are observed accompanying the convulsion of idio-

pathic epilepsy. Although the circulatory and respiratory changes associated with the picrotoxin convulsion are not exactly similar to those found in idiopathic epileptic convulsions, yet the independent presence of blood pressure change associated with picrotoxin convulsions tends to show that these changes are part of the convulsion alike in picrotoxin and idiopathic epileptic convulsions.

From the facts that there exist medullary convulsants and that their ensuing convulsions are associated with symptoms of disturbance of the autonomic nervous system similar to those found in idiopathic epileptic convulsions, and with circulatory disturbances analagous to those found in idiopathic epileptic convulsions, we conclude that we have further evidence that the site of discharge of the convulsion in some types of idiopathic epilepsy is in the medulla and pons. The medulla and pons participate in the convulsion in all cases of epilepsy whether the site of discharge is here or not.

25 East Washington Street.