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THE ACTION OF STRYCHNINE ON HERING-BREUER REFLEXES.

By R. S. CREED, *Fellow of New College,*
and D. H. HERTZ, *Rowdon Scholar of New College.*

(*From the Department of Physiology, Oxford.*)

In 1911 Owen and Sherrington were unable to reach a decision on the question whether strychnine acts by transforming the process of central inhibition into one of central excitation or by selectively raising the responsiveness of reflex arcs to excitatory, but not, or not to the same extent, to inhibitory influences. On either view a ready explanation is found for the familiar reversal of inhibitory reflex effects when these are evoked by stimulation of a large nerve trunk containing a mixture of afferent fibres, the majority of which are potentially inhibitory, while a few are potentially excitatory, with respect to a given test muscle.

More than ten years later, Bremer [1922, 1925] found that the inhibitory effects of stimulating the cortex of the anterior lobe of the cerebellum are neither reversed nor diminished by strychnine. This has been confirmed by Miller [1926]. Bremer was therefore led to the conclusion that strychnine "reversal" is an expression of the stimulation of mixed afferent nerves, and that the action of the drug is not to convert the central process of inhibition into excitation but merely to increase enormously the excitability of motor arcs. On a purely inhibitory reflex strychnine is devoid of influence. In support of his contention he quotes the finding of Magnus and Wolf [1913] that inhibition of triceps brachii and of vastocrureus in tonic neck and labyrinthine reflexes is not reversed by strychnine.

Further examples of the absence of reversal in reflexes in which there is reason to believe that a homogeneous set of receptors is alone involved have since been brought to light. Liddell and Sherrington [1925] noted the continued inhibition of the stretch reflex of quadriceps on passive stretch of a knee flexor after the administration to decerebrate cats of 0·25 mg. of strychnine per kg. body weight. Less than one-third of this dose will cause "reversal" on stimulation of a bared afferent nerve.

Cooper and Creed [1927] obtained similar results when studying the relaxation of quadriceps evoked reflexly by active contraction of hamstrings. The work of Matthews [1931] makes it probable that the receptors involved in the latter experiments were muscle spindles.

The mode of action of strychnine becomes of considerable importance when one reflects that the conversion of central inhibition into central excitation would, if true, form an important datum in any discussion of the intimate nature of these two processes. It occurred to us that a simple method of providing additional evidence would be to test the action of the alkaloid on the relaxation of the inspiratory muscles which results from distension of the lungs. This vagal reflex was first described as a feature of "the self-regulation" of respiratory movements by Hering and Breuer [1868] and has been repeatedly confirmed by subsequent workers. It would seem to offer an unusually good opportunity of applying a normal adequate stimulus to a presumably homogeneous set of receptors. The diaphragm-slip technique of Head [1889] provided a suitable method of recording the movements of an inspiratory muscle during normal breathing.

Seemann [1910] noted that after giving rabbits strychnine "expiratory spasm from inflation of the lungs is much more powerful than before." He did not, however, record the movements of inspiratory muscles, and in other respiratory reflexes describes the occurrence of strychnine "reversal."

Method.

Rabbits have been used for all experiments on account of the ease with which their powerful diaphragm slips can be isolated for recording. Under deep anæsthesia (ether), Head's technique for preparing a diaphragm slip has been closely followed. That of the left side only was used. Its upper end was fixed to the chest wall by passing a loop of thread through a button on the abdominal surface of the diaphragm and knotting the ends in front over one of the lower costal cartilages. The lower end of the slip was left attached to part of the ensiform cartilage.

In the left hindlimb the nerve to hamstrings was cut. The sciatic nerve in this limb was also cut just above the knee and its central end prepared for stimulation. All movements of the ankle were thereby prevented, and active extension only was possible at the knee. Both carotid arteries were ligated and a tracheal cannula was inserted. The animal was then decerebrated through the midbrain by the trephine method and the anæsthesia discontinued.

Two hours later, when the ether had been blown off in the course of natural breathing, the preparation was transferred to the recording apparatus. Here it was tied supine. Movements of the fixed end of the slip were prevented by clamping the sternum and lower costal cartilages of the right side and rigidly attaching the clamp to the table top. The piece of ensiform cartilage into which the other end of the slip was inserted was connected by thread with a light lever writing on smoked paper. Care was taken that the slip had a free pull, clear of the liver and other obstructions. Except when observations were actually being made, it was packed in warm swabs wrung out of saline.

Artificial inflation or deflation of the lungs was brought about by one of the experimenters blowing or sucking through the tracheal cannula. The cannula was connected by a T-piece with a mercury manometer fitted with a float carrying a writing point. By this means the changes of intrapulmonary pressure were signalled on the moving smoked paper. A time marker recorded seconds.

General observations.

In good preparations it was easy to obtain satisfactory records from the diaphragm slip of normal inspiratory contractions and expiratory relaxations. Very occasionally no movements could be observed although the animal appeared to be breathing normally. In these cases the nerve supply or blood supply of the slip had probably been damaged during the operation [cf. Head, 1889]. After successive administrations *per venam* of a 0·02 p.c. solution of strychnine hydrochloride, the movements thus recorded became more ample. We have no precise data as to the extent of this increase in the excursions, because the lever was detached from the slip while each injection was being made. But it was commonly well marked, and, for convenience in recording, the magnification of the excursions of the writing point was progressively diminished during an experiment. Wood and Cerna [1892], Impens [1899], Biberfeld [1904], and Cushny [1913] all agree that strychnine greatly increases the respiratory exchange. The last named, however, using both anæsthetized and decerebrate rabbits, differs from the others in finding the rate only of the breathing to be affected, while the depth is unchanged or even diminished. Our findings do not support him. Initially, the breathing of our preparations was often at as high a rate as 100 per min. Subconvulsive doses of strychnine caused no increase, and sometimes a decrease, in this frequency. Doubtless the result might have been different on the intact or anæsthetized animal with a slower rate of breathing.

At the beginning of an experiment, stimulation of the prepared central end of the left sciatic nerve with weak induction shocks caused that knee, if tonically extended, to relax. Flexion of the hip regularly occurred and was frequently followed by powerful movements of progression in which all the four limbs participated. When strychnine had been injected intravenously in amounts exceeding 0·1 mg. per kg., similar stimulation of the sciatic nerve evoked obvious contraction in quadriceps extensor.

Between successive injections of strychnine the effects on the diaphragm slip of inflation and deflation of the lungs were recorded. The administration of the drug was continued until death supervened. The lethal dose in our preparations has usually been between 0·15 and 0·2 mg. per kg. body weight. Once opisthotonus and death have resulted from 0·1 mg. per kg., and once a dose of 0·2 mg. per kg. failed to kill while 0·225 did so. In the intact rabbit Maurel [1908] found 0·5 mg. per kg. *intra venam* to be always fatal, and 0·2 mg. to be never fatal. Our lower figures are probably attributable to the enhanced reflex excitability of decerebrate as compared with intact animals, and their consequent oversensitiveness to strychnine [cf. Cushny, 1913].

Our experience agrees with the statement of Poulsson [1920] that death is ushered in by only a single generalized convulsion, comprising opisthotonus and maintained extension of all the limbs. With sub-lethal doses there is, of course, abundant evidence of increased excitability, *e.g.* to blowing on the skin, and widespread convulsive jerks are readily induced. Very occasionally we have seen recovery from opisthotonus of several seconds' duration, but it has not in these cases been accompanied by full extension of the limbs.

Effect of inflation of the lungs.

The effect of raising the intrapulmonary pressure by 1–3 cm. Hg is cessation of respiratory movement with relaxation of the diaphragm slip. Our findings agree with Head's in that the inhibitory pause may be preceded by an inspiration if the inflation is made suddenly. Thereafter the cessation of movement has generally, in our experience, been maintained throughout the longest periods of inflation that we have used (7 sec.).

The relaxation of the slip is no less marked after maximal doses of strychnine. Thus, to quote one of several similar experiments, 0·9 c.c. of a 0·02 p.c. solution of strychnine was injected into the femoral vein of a rabbit weighing 1800 g. Stimulation of the central stump of the left

sciatic nerve by weak induction shocks then evoked extension of the left knee, often followed by galloping movements. But even after two subse-

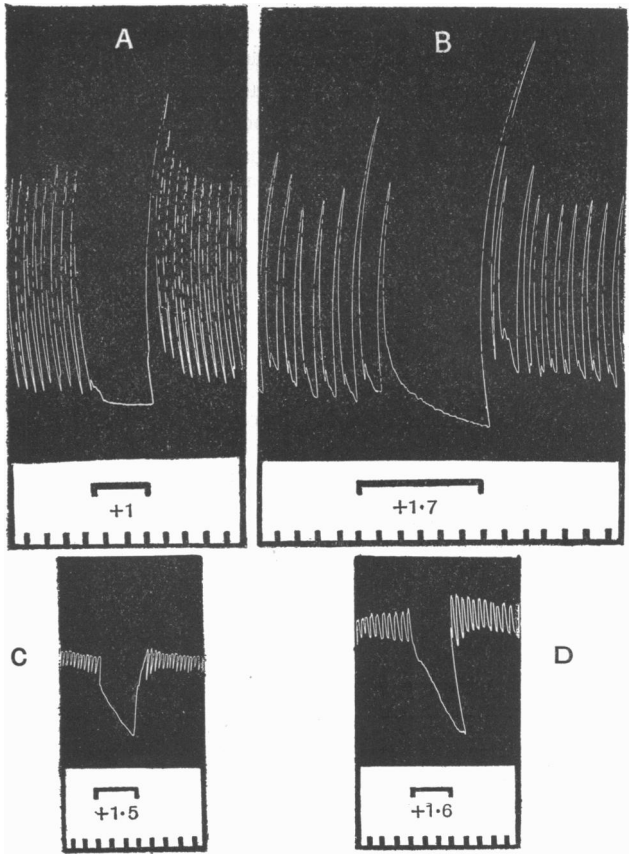

Fig. 1. Tracings from diaphragm slip of decerebrate rabbit. Inspiratory contractions upwards; expiratory relaxations downwards. The signal indicates the duration and the extent of artificial inflations of the lungs. The time marker gives seconds. A. Rabbit weighing 1800 g. 3 hours after decerebration. Intrapulmonary pressure raised by 1 cm. Hg. B. The same animal an hour later, after being given 0·17 mg. of strychnine per kg. body weight. Further 0·03 mg. was fatal. C. Another rabbit weighing 2400 g. Interval after decerebration 2½ hours. The diaphragm is evidently not fully relaxed in the expiratory phase of normal breathing. D. The same animal an hour later, after being given 0·2 mg. of strychnine per kg. body weight. Further 0·025 mg. was fatal.

quent injections, each of 0·3 c.c., the slip relaxed on inflation of the lungs (Fig. 1). A further 0·3 c.c. caused opisthotonus and death. Coincident with inhibition of the slip, contraction of the abdominal muscles has often

been noticed. This is obviously exaggerated under the influence of strychnine.

Although cessation of all respiratory movement has usually occurred both before and after giving strychnine, in one experiment the cessation appeared not always to be complete following very large doses of the drug. But even then the pauses between successive inspirations were much prolonged, and the level of the writing point in the expiratory position was slightly, and in the inspiratory position greatly, reduced. This isolated observation can be explained either by increased sensitivity of the poisoned respiratory centre to its normal stimuli (of which we have already produced evidence), or, less probably, by analogy with Langley's finding [1913] that vagal vaso-motor reflexes may be paralysed by giving a rabbit enormous doses (2 mg.) of strychnine. Scott [1925] has shown, by local application of the drug to the floor of the fourth ventricle, that this is due to a blocking of the reflex path in the medulla oblongata.

Be this as it may, there seems no room for doubt that, even when apparent reversal of the effect of sciatic stimulation is well marked, strychnine causes no reversal of the normal inhibitory relaxation of the diaphragm elicited by inflation of the lungs. The action of the drug therefore cannot be to convert central inhibition into central excitation.

Effect of deflation of the lungs.

Although the few observations to be reported under this heading have little bearing on our main theme, they seem worthy of record as helping to clear up certain points which have recently been raised in regard to respiratory reflexes. The intrapulmonary pressure has usually been lowered by about 3 cm. Hg by sucking air from the tracheal cannula; sometimes much larger and sometimes much smaller differences of pressure between the outside of the thorax and the pulmonary air spaces have been established.

No attempt will be made to deal fully with the extensive literature on the subject. This has lately been well summarized by Hammouda and Wilson [1932] and by Sharpey-Schafer [1932].

(1) *Influence on the tonus of the diaphragm.*

Deflations of from 0·8 to 6·5 cm. Hg have invariably been accompanied by a rise of tonus as evidenced by a higher level in the record traced by the diaphragm slip. The extent of this effect varies considerably n different preparations. As a rule it is much less marked after large

doses of strychnine, perhaps because the "normal" tonus of the inspiratory muscles is then raised almost to maximal degree.

Hammouda and Wilson [1932] disagree with Hering and Breuer, with Head, and with many other workers whom they quote, in finding no indication of any active inspiratory response to collapse. Their failure to observe the reaction is not surprising since the method they used gives no information regarding the condition of individual muscles. Collapse was induced by raising the pressure of the air surrounding the body of the animal (dog) by amounts varying from a few mm. to 90 mm. Hg, while the trachea communicated directly with air at atmospheric pressure. The records indicate the volume of air in the lungs at any given moment. With raised external pressure this volume may be expected to remain below normal even though the inspiratory muscles are contracting in a vain attempt to counteract the deflation. Our observations confirm the classical view that there is, in fact, an inspiratory response to deflation.

(2) *Influence on the rhythm of respiration.*

On causing collapse of the lungs by puncture of the pleuræ, Hering and Breuer and later Head reported long-lasting cessation of respiratory movement with spasm of the diaphragm. In one of Head's tracings from a diaphragm slip there is marked slowing of respiratory movement during closure of a rabbit's trachea at the end of normal expiration. Sharpey-Schafer and Bain [1932] have also published records showing a diminished frequency of respiration on closing the tracheæ of narcotized dogs at the height of the expiratory phase of normal breathing. On the other hand, their tracings of respiratory movements on lowering the intrapulmonary pressure by connecting the trachea with a large reservoir of air 1–2·2 cm. Hg below atmospheric pressure exhibit a quickening in the rate of breathing. Similarly Hammouda and Wilson, by the method already described, find that in dogs "collapse of the lungs beyond the normal position of equilibrium is accompanied by an increase in the rate of breathing proportional to the diminution in lung volume," and that this effect is abolished by section of both vagi.

At first sight, the former conclusions appeared to be confirmed, and the latter to be contradicted, by our observations. We have nearly always found slowing, though not complete stoppage, of diaphragmatic movement as the result of sucking air from the lungs of rabbits (Fig. 2). Strychnine has generally accentuated the effect. Further examination of the records, however, shows that the cases in which this occurs are those in which the intrapulmonary pressure has been reduced by more

than 2 cm. Hg (in one case 1 cm. gave slight slowing). Reductions of from 0·8 to 1·6 cm. Hg have usually resulted in a quickening of the rate even when greater reductions cause slowing. In the experiments on

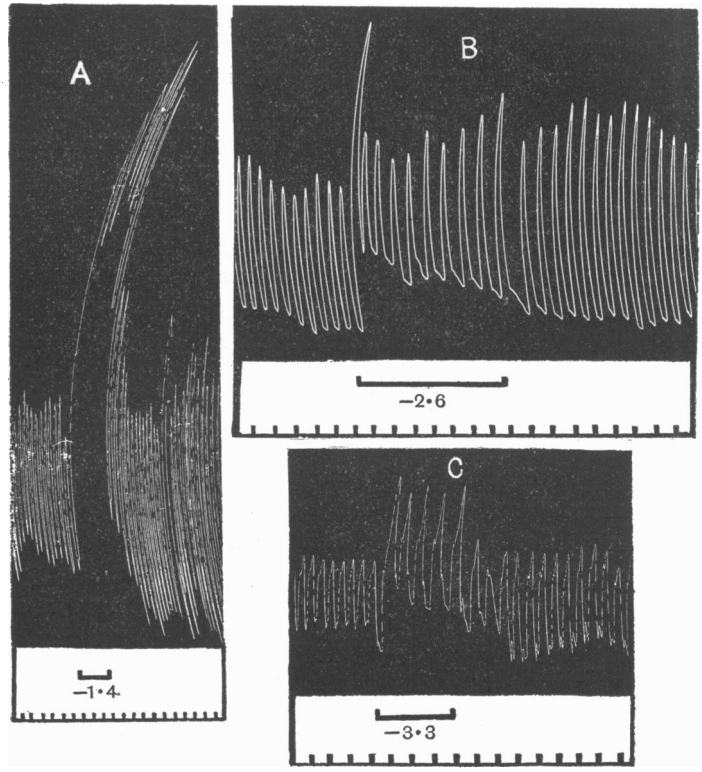

Fig. 2. Tracings showing the effect of deflation of the lungs. A. Rabbit weighing 2550 g. decerebrated 3 hours before. (It has been given 0·05 mg. of strychnine per kg. body weight.) Intrapulmonary pressure lowered by 1·4 cm. Hg. The frequency of the breathing is scarcely affected. The same reduction of pressure before strychnine caused definite quickening. Marked increase in tonus of the slip. B. Rabbit weighing 1800 g. decerebrated 4 hours before. (It has been given 0·13 mg. of strychnine per kg. body weight.) Reduction of intrapulmonary pressure by 2·6 cm. Hg causes obvious slowing. C. Rabbit weighing 1900 g. decerebrated 3 hours before. (No strychnine has yet been administered.) The frequency of the breathing is diminished and the amplitude of the excursions is increased by the deflation.

which Hammouda and Wilson base their conclusion that collapse induces increase in the rate of breathing, the excess of external over intrapulmonary pressure appears not to have exceeded 1·4 cm. Hg.

It therefore looks as though the influence of deflation on rhythm depends upon the extent of the deflation. Small deflations evoke increase, and large deflations evoke decrease, in the rate of breathing. That the latter is not due to absurdly intense stimulation is indicated by the facts (1) that our deflations were induced by volitional contractions of the inspiratory muscles of the experimenter, and (2) that occlusion of the trachea at the end of normal expiration undoubtedly occasions slowing. Whether the opposed effects are due to stimulation of two distinct sets of vagal endings; or to differences in the relative preponderance of vagal influences (*a*) on Hering-Breuer reflexes and (*b*) on the inherent rhythmicity of the respiratory centre [cf. Hammouda and Wilson, 1932]; or to the different effects of vagal and proprioceptive reflexes [see Boothby and Berry, 1915; Fleisch, 1928; Hammouda and Wilson, 1932; Sharpey-Schafer and Bain, 1932], we have no evidence. The decerebrate rabbit is so delicate a preparation that it would almost certainly die were its vagi divided. Study of other workers' results, however, leaves little room for doubt that there are afferent paths for both responses in the vagi. The matter is of some academic interest and would be worth pursuing further. But in ordinary circumstances a difference between intrapulmonary and external air pressures, with consequent alteration in the mean state of expansion of the lungs, must be of rare occurrence. The investigation would probably throw little light on the normal regulation of the frequency of respiration.

(3) *Influence on the amplitude of diaphragmatic contractions.*

The changes in amplitude resulting from pulmonary deflation are not, in our experience, constant. When the rise in tonus has been great, there has generally been a tendency to maintained contraction, and the respiratory excursions of the lever have been smaller than normal. On the other hand, when tonus has been little affected, not only are the excursions less frequent than normal, but their amplitude is often increased (cf. Head's Pl. 1, Curve viii).

With the dog's trachea closed at the end of expiration, Sharpey-Schafer and Bain [1932] record diminished movement of the epigastrium. This, however, should not be regarded as conclusive evidence of diminished diaphragmatic activity. If the force of the rhythmical contractions remained unaltered, the epigastrium would still be expected to move less than it normally does. For movement would now be opposed by the lowering of intrapulmonary pressure consequent on contraction of inspiratory muscles with no entry of air into the lungs. Nor is it

justifiable, in our opinion, to draw quantitative conclusions regarding the degree of activity of the inspiratory muscles as a whole from observations, during closure of the trachea, of the respiratory waves on a tracing of the blood-pressure. These waves depend mainly, it is thought, on changes in the mediastinal pressure, and with equal inspiratory efforts such changes will clearly be greater when the trachea is closed than when it is open.

SUMMARY.

1. Relaxation of a rabbit's diaphragm slip, evoked by inflation of the lungs, is never replaced by contraction as a result of administering strychnine. This finding supports Bremer's conclusion that the action of strychnine is not to convert central inhibition into central excitation, but to facilitate the passage of excitatory processes through reflex arcs.

2. Under strychnine, the amplitude of respiratory movements of the diaphragm is increased in the decerebrate preparation. The frequency is not increased.

3. The lethal dose of strychnine for the decerebrate rabbit is usually between 0·15 and 0·2 mg. per kg. body weight.

4. Deflation of the rabbit's lungs causes increased tonus of the diaphragm slip. When the intrapulmonary pressure is reduced by more than 2 cm. Hg the breathing becomes slower than normal; with smaller reductions of pressure, quickening occurs. Deflation has a variable influence on the amplitude of diaphragmatic contractions. These effects are compared with the findings of other workers who have often reached mutually contradictory conclusions.

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