

OBSERVATIONS ON STRYCHNINE REVERSAL. By
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I. STRYCHNINE AND FLEXOR INHIBITION.

THAT strychnine changes an inhibitory reflex to an excitatory was shown in previous papers¹ chiefly by use of the knee extensor muscle *vastocrureus*. Incidental examination of the effect of strychnine on the reflex action of a flexor muscle² tended to show that there also it converts inhibitory effect into excitatory. We have now with improved procedure returned to this point, using the main flexor of the knee, *semitendinosus*.

Our experiments have been made on the cat deeply anæsthetised until decerebration had been performed. In the decerebrate preparation the *semitendinosus*, the chief knee flexor, is isolated by appropriate nerve-sections³ and detachment of other muscles so that it remains the only unparalysed muscle in the limb. The muscle is dissected out for its distal two-thirds; its nerve and blood supply enter above and remain intact. The opposite fellow limb is entirely immobilised by severance of all its nerves. The preparation being placed supine the pelvis, both femora, and both tibiæ are fixed by drills held in rigid supports firmly attached to the experiment table. The hind-limbs are thus immobilised with hip and knee joints semiflexed. The tendon of the *semitendinosus* under examination is then attached by a thread to a horizontal myograph. A pair of non-polarisable electrodes is applied to the central stump of the combined peroneal-popliteal nerve-trunk

¹ *Roy. Soc. Proc. B.* LXXVI. 288. 1905; this *Journal*, xxxvi. 191. 1907.

² *Roy. Soc. Proc. B.* LXXXI. 252. 1909.

³ Cf. Sherrington and Sowton. *Roy. Soc. Proc. B.* LXXXIV. 201. 1911.

of each limb close above the nerve severance at the knee. For stimulation we have employed faradism with an inductorium of the Berne pattern for contralateral nerve and an Elliot inductorium for the ipsilateral nerve. The ipsilateral nerve gives reflex contraction of the muscle, the contralateral gives reflex inhibition. By means of the ipsilateral nerve a background of contraction is obtained against which the inhibitory relaxation induced by the contralateral nerve can be seen.

The effect of intercurrent stimulation of the inhibitory (contralateral) nerve before and after intravenous injection of .3 mgm. strychnine hydrochloride shows the result exhibited in Fig. 1, A, B, and C. The inhibitory notch produced in the contraction background

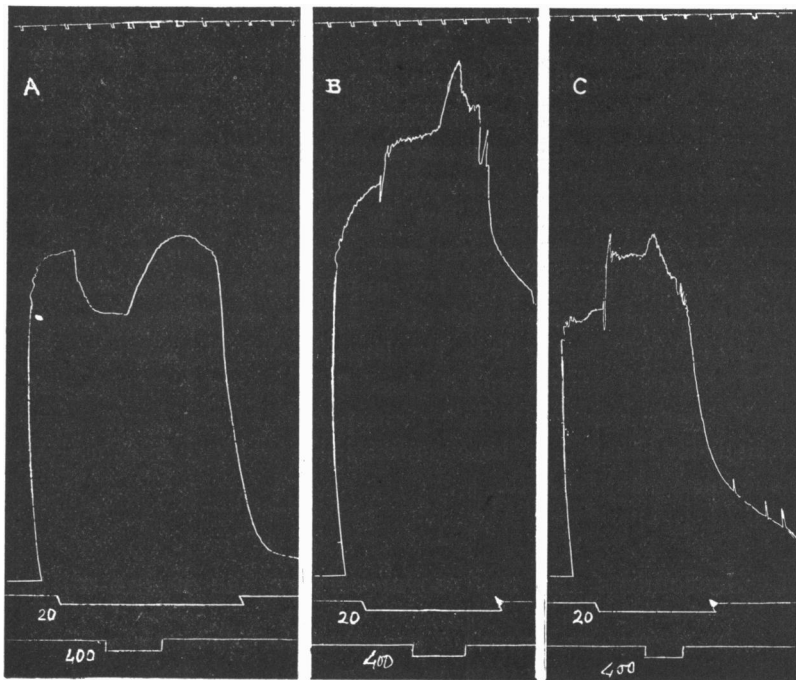


Fig. 1. Flexor preparation; *semitendinosus*: ipsilateral peroneal, upper signal; contralateral peroneal lower signal. Between A and B strychnine hydrochl. .3 milligram given *per venam*.

by contralateral stimulation prior to strychnine is replaced after strychnine by an ascent marking augmented contraction. The drug reverses the character of the contralateral reflex from depressor to pressor effect.

That strychnine reversal holds for inhibition of flexor centres as well as of extensor has interest in the following connection. Concurrent

stimulation of a reflex centre by two or more afferents of opposed effect probably approaches natural conditions of reaction more nearly than does stimulation from one afferent source alone¹. The latter can hardly ever naturally occur. The centre governing twin antagonistic muscles can easily by experiment be thrown under the joint influence of two afferents of opposed effect upon it. It is then found² that the opposed influences, pressor and depressor, act jointly on each of the twin muscles. In short, double reciprocal innervation comes to work. In the case of any one simple reciprocal (\pm) reflex such as is evoked by stimulation of a single reflex source alone the strychnine effect is confined to making that one of the two opposed muscles which normally relaxes contract instead of relaxing. Thus, to take the case of reflex flexion of the knee from simple stimulation of the foot, the disturbance wrought by strychnine is that the extensor instead of being relaxed by inhibition is excited to contract and opposes instead of yielding to the flexor, and if the more powerful muscle may overcome the flexor so that extension instead of flexion results. But in the case of double reciprocal innervation the disturbance is more complex. Thus, to take reflex flexion of knee produced by two appropriately graded stimulations applied concurrently one to each foot. In this case what happens under strychnine is that not only is the large inhibitory component in the central taxis of knee extensor changed from - sign to + sign, but the similar though smaller inhibitory component in the flexor's taxis is also similarly changed. The co-ordinative grading is upset not merely for one muscle but for both.

II. STRYCHNINE AND THE PROPRIOCEPTIVE ARC OF THE MUSCLE.

1. *Strychnine converts a proprioceptive inhibitory reflex into an excitatory.*

The afferent nerve-fibres belonging to a skeletal muscle are found to influence powerfully the moto-neurones innervating their own muscle³. With flexor muscles this influence is excitatory⁴; with extensors it is, when examined by direct stimulation mechanical or faradic of the bared nerve, preponderantly inhibitory⁵. The direct agent of stimulation of

¹ Sherrington. *Integrative Action of Nervous System*, 182. 1906.

² *Roy. Soc. Proc. B.* LXXXI. 259. 1909.

³ *Ibid.* B. LXXXIX. 340. 1907.

⁴ *Ibid.*

⁵ *Ibid.*

these muscle-afferents being under natural conditions the muscle itself, they come under that class of receptive nerves which has been termed *proprioceptive*¹. The following experiments were directed toward determining whether strychnine can reverse the inhibitory action of the proprioceptive arc and if so whether strychnine reversal of skeletal inhibition in general may be traced to its action on the proprioceptive arc.

As regards the proprioceptive arc of an extensor, the ankle-extensor *gastrocnemius* allows experimentation of this kind more readily than does the knee-extensor *vastocrureus*². The nerve of the former at some distance above entering the muscle bifurcates into divisions which pass separately to the muscle's mesial and lateral heads respectively. One of these divisions severed at entrance into the muscle and carefully isolated from its fellow nerve furnishes a slender nerve some 6 cm. long (cat). By stimulating this close above its cut end the reflex effect of its afferent fibres can be examined. If all other nerves of the limb have been severed excepting only that to the other head of the *gastrocnemius* the experiment examines the reflex effect of the afferents of the one head of the muscle upon the moto-neurones of the other head. The effect then usually seen is inhibition. And the same has been shown in a similar manner for other extensor muscles, namely *vastocrureus* in hind-limb and *triceps brachii* in fore-limb³. But in these latter cases mechanical stimulation only can be used since the afferent nerves are not long enough for applying electrical stimuli without risk of spread of current to the rest of the muscle's nerve. In the *gastrocnemius* preparation there is little fear of this complication. In the decerebrate preparation the inhibitory effect is easily seen since the tonus of the muscle renders the inhibitory relaxation obvious. The inhibitory relaxation is often followed on withdrawal of the stimulus by rebound⁴ contraction; the total reflex reaction is then diphasic (- +). The rebound as a rule quickly tires out; when the reaction is repeated a few times at short interval the rebound wanes and temporarily disappears, to reappear after a period of rest.

Whether the reflex inhibition is or is not followed by rebound, a small dose of strychnine does away with the inhibition phase of the reaction and replaces it by contraction. This reversal from depressor to pressor effect ensues in a few seconds after intravenous injection of .3 mgm. strychnine hydrochloride in a 2 kil. cat.

¹ Sherrington. *Integrative Action of the Nervous System*. 1906.

² *Roy. Soc. Proc. B.* LXXIX. 339. 1907.

³ *Ibid.* 340. 1907.

⁴ *Ibid.* B. LXXVII. 486. 1905.

2. *Strychnine converts an inhibitory reflex into an excitatory in spite of section of the proprioceptive afferents of the reacting muscle.*

A fact to be remembered in regard to strychnine reversal is that pointed out by Seemann¹ who examined the influence of the drug on the expiratory reflex evoked by NH₃ vapour. He showed that there strychnine reverses the expiratory reflex to an inspiratory one, upsetting at once its fundamental coordination and its protective efficacy. The afferent nerve of this reflex is trigeminus², but Seemann found the reversal occur only so long as vagus remained uncut, that is so long as the reflex tonus of the respiratory centre due to vagus remained. This interesting observation raises the question whether the inhibitory reflex of an extensor muscle will be reversed by strychnine when the reflex tonus of the muscle has been abrogated by cutting the reflex arc productive of that tonus. Strychnine increases the vagus tonus³ and it increases the reflex tonus of the extensor limb muscle. This increase can often be seen to forerun the reflex reversal. Moreover it has been recently shown⁴ that increase of the reflex excitation of a flexor centre by one afferent may change the effect of another afferent, inter-currently brought to play on it, from inhibition to excitation.

The afferent limb of the arc on which depends the reflex tonus of the extensor muscle comes from the muscle itself⁵ and passes through the afferent spinal roots of the local segments to embouch through intermediate intraspinal neurones⁶ on the moto-neurones of the muscle. The arc can therefore be broken in its afferent course by sectioning the appropriate afferent spinal roots⁷. When this is done the reflex tonus is set aside, judging (1) by the flaccid condition of the resting muscle, (2) by the loss of knee jerk, (3) by the non-appearance of postural tonus in the muscle after decerebration. For our observations (cat) we have used the knee extensor, *vastocrureus*, and have severed the afferent roots of the 2nd, 3rd, 4th, 5th, and 6th post-thoracic nerves of the side

¹ J. Seemann. *Ztsch. f. Biol.* LIV. 153. 1910.

² Kratzschmer. *Sitz. d. Wien. Akad.* 2. Abth. LXII. 147. 1870; Seemann. *Pflüger's Arch.* xci. 314. 1902.

³ Seemann. *Ztsch. f. Biol.* LIV. 153. 1910; also *Pflüger's Arch.* xci. 332. 1902.

⁴ Sherrington and Sowton. *Roy. Soc. Proc. B.* LXXXIV. 201. 1911.

⁵ *Roy. Soc. Proc. B.* LXXIX. 345. 1907.

⁶ Baglioni. *Arch. f. Physiol.* Supp. B, 193. 1900.

⁷ The appropriate roots (cat) are 4th and 5th or 5th and 6th post thoracic according as the plexus is pre-fixed or post-fixed; cf. this *Journal*, XIII. 640. 1892.

to which the muscle taken belonged. In most cases this severance was performed a couple of hours previous to the observations. In one case however the severance was made ten months prior to the observations. In all cases the preparation was decerebrate and in three cases the cord was transected as well, the level of transection being between the 2nd and 3rd post-thoracic segments. All the peripheral nerve-trunks of both hind-limbs were cut excepting only the nerve of the vastocrureus muscle itself under observation. The spinal cord was transected about an hour before the observations were made.

With the deafferented muscle, as with the undeafferented, the ipsilateral limb afferents such as peroneal and popliteal still exert their usual inhibitory influence. This can be ascertained by testing them upon reflex contraction of the muscle evoked by stimulation of afferents of the contralateral limb. With the vastocrureus thus deafferented administration of strychnine in the usual small dose at once changed the inhibitory effect of the ipsilateral afferents to an excitatory one. In this case therefore the tonic action of the arc on which the reflex tonus of the muscle depends is not a necessary condition for the appearance of the strychnine reversal.

III. STRYCHNINE AND THE IPSILATERAL LIMB REFLEX ON GASTROCNEMIUS.

Finally we have extended to gastrocnemius (cat) observations of the kind made originally on vastocrureus, hoping for further insight into the manner in which the strychnine reversal takes place. Our preparations were decerebrate and similar to that described above in § II, except that the whole nerve of the gastrocnemius of one limb remained intact and the afferent nerve used was ipsilateral peroneal severed and stimulated at the outer side of the knee. Gastrocnemius differs from vastocrureus in being a double-joint muscle. It is an extensor of ankle and in addition potentially a flexor of knee. But experimental analysis of its *role* in various reflexes has shown that in them the reflex nervous taxis treats gastrocnemius as an extensor and deals with it as with the other extensors and not as a flexor. Before administration of strychnine the reflex effect on the muscle given by our stimulations (faradic) was invariably inhibition (Fig. 2 A, and Fig. 3 A) followed usually by rebound contraction on cessation of the stimulus (Fig. 3 A).

Intravenous injection of .3 to .5 mgm. strychnine hydrochloride always rapidly changed this inhibitory effect into excitation (Fig. 2 *B*). Occasionally the change was sufficiently slow in its progress to allow the tracing by the myograph of a sequence of intermediate stages in the transition from normal to full reversal (Fig. 3). It was seen that, as observed previously with vastocrureus, an early feature in the transition is the appearance of an initial brief contraction (Fig. 3 *C* and *D*) preceding an inhibitory relaxation, the latter similar to though

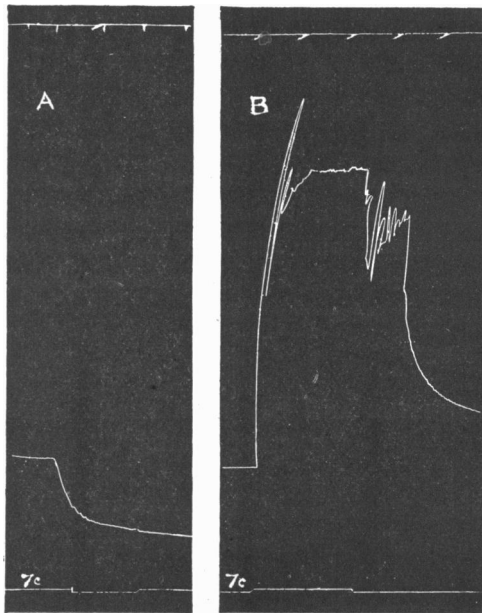


Fig. 2. *Gastrocnemius* preparation: ipsilateral peroneal. Between *A* and *B* strychnine hydrochl. .3 milligram given *per venam*.

less than that of the normal reflex. When the reflex is excited again at few seconds' interval this initial contraction is more marked in amplitude and duration at the expense as it were of the inhibitory relaxation. Finally the latter disappears and is replaced by contraction (Fig. 3 *E*, *F*). In the earlier stages of the transition the rebound contraction following withdrawal of the stimulus is greater (Fig. 3 *B*) than usual; in the final stage it is usually altogether absent (Fig. 2 *B*), as was seen previously with vastocrureus¹.

¹ *This Journal*, xxxvi. 191. 1907.

One character of the transition is that the new feature, contraction, first intrudes itself as an initial event briefly forerunning such of the normal inhibitory relaxation as at that time still persists. Now, in the unstrychnised decerebrate preparation the reflex response of the extensor (*vastocrureus*) to its own limb's afferents shows¹ under certain circumstances some initial contraction preceding the inhibitory relaxation. This contraction it is true occurs only under particular conditions, but that it occurs suggests that these afferent trunks contain besides depressor

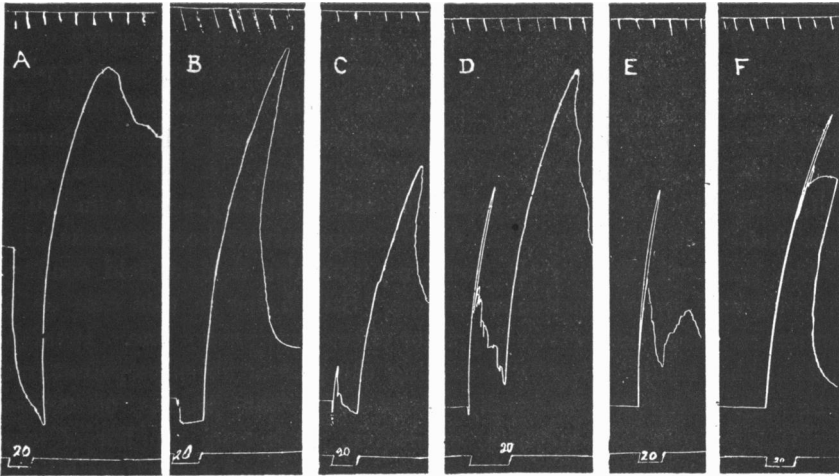


Fig. 3. *Gastrocnemius* preparation; ipsilateral peroneal. Between A and B strychnine hydrochl. .5 milligram given *per venam*.

fibres others which are pressor. Strychnine may therefore conceivably reverse the ordinary reflex effect by raising centrally the relative efficiency of pressor fibres commingled with the depressor ordinarily prepotent. In fact in all these cases of reversal whether of unstrychnised or strychnised preparations the question rises whether the reversal is traceable to the raising of the potency of one set of fibres in a mixture containing two of opposed effect, or whether the determinant condition, for instance strychnine, actually changes the central action of one and the same afferent fibre from depressor to pressor or in

¹ Sherrington and Sowton. *Roy. Soc. Proc. B.* LXXXIII. 435. 1911.

the case of chloroform (Bayliss¹) from pressor to depressor. It would help decision between the two possibilities were some afferent nerve available which in the unstrychnised preparation invariably produced on a particular muscle inhibition alone under all circumstances. In the limb region such a nerve seems difficult to find². With the gastrocnemius for instance the muscle's own afferent nerve when bared and stimulated usually evokes inhibition in the unstrychnised decerebrate preparation, yet occasionally it evokes excitation, *i.e.* has a pressor effect instead of a depressor. This contraction is not referable to escape of the stimulus to motor fibres in the uncut twin branch of the nerve for it occurs with mechanical stimulation (ligation) as well as with electrical. Indeed the afferent nerve of an extensor muscle, though commonly depressor to its own muscle when artificially stimulated, must yet commonly exert pressor action on the muscle to judge from its being the main or only afferent channel essential to the muscle's natural reflex tonus. In this case again therefore two sets of fibres, inhibitory and excitatory, seem admixed in the small afferent nerve, a nerve of comparatively homogeneous kind since gathered up entirely from one muscular field, a field confined to one half of one particular muscle. Strychnine in this case as in others replaces the nerve's depressor effect by a pressor one. It might attain this result either by rendering the pressor fibres prepotent over the depressor, or by actually transforming the process of central inhibition into one of central excitation. A certain number of facts may be marshalled both for and against each of these possibilities, but at present the evidence does not appear decisive either way. The question seems hardly ripe for fruitful discussion now.

GENERAL CONCLUSIONS.

1. The reversal by strychnine of inhibitory to excitatory reflex effect obtains in the case of the flexor muscle (knee-flexor) as well as in the case of the extensor (knee-extensor).
2. As tested on gastrocnemius the reversal occurs with the inhibitory reflex given by the proprioceptive nerve of the muscle itself as well as with other reflexes inhibiting that muscle.

¹ Bayliss. *This Journal*, xiv. 316. 1893, and *Roy. Soc. Proc. B.* LXXXIII. 365. 1908. Sherrington and Sowton. *This Journal*, XLII. 383. 1911.

² Sherrington and Sowton. *Roy. Soc. Proc. B.* LXXXIII. 435, and LXXXIV. 201. 1911.

3. The reversal occurs with the deafferented extensor as with the normal, in the spinal preparation as in the decerebrate.

4. The reversal obtains with the ankle-extensor as with the knee-extensor.

5. There is some evidence indicating that the afferent nerves employed for evoking these reflexes contain fibres of excitatory as well as fibres of inhibitory effect. It is possible therefore that the reversal produced by strychnine in these cases is due to the drug favouring the central action of the former fibres and depressing that of the latter. But there are difficulties for this view, and on the other hand the drug may centrally transform the essential process of inhibition into an excitatory process. There does not seem sufficient evidence as yet for deciding between these two possibilities.