Further observations and experiments regarding the true nature of tetanus / by Sydney Ringer and William Murrell.

[From the *Journal of Anatomy and Physiology*, Vol. XI.]

5.

FURTHER OBSERVATIONS AND EXPERIMENTS REGARDING THE TRUE NATURE OF TETANUS.

By SYDNEY RINGER, M.D., *Professor of Therapeutics at University College*, and WILLIAM MURRELL, L.R.C.P., *Medical Registrar at Westminster Hospital.*

IN a paper published in the Medico-Chirurgical Transactions for 1876, we controverted the view commonly accepted that tetanus is always due to increased excitability of the spinal cord, and we detailed numerous experiments to prove that in tetanus the resistance of the cord is diminished or destroyed, so that an impression conveyed by an afferent nerve can spread throughout the reflex portion of the central nervous system and produce tetanus. Many persons having expressed strong doubt as to the existence of this "resistance," we propose now to give the reasons for our belief in this property, and to shew that it is not fixed, nor unmodifiable, but that probably disease, certainly some drugs, will weaken or destroy it, the other functions of the cord meanwhile remaining unimpaired or but slightly depressed.

We first draw attention to the fact that this resistance is recognised in recent works on Physiology. Thus Hermann says, resistance of the cord is lessened in tetanus, and Ferrier, that in strychnia tetanus "the resistance to radiation is diminished." This view, however, is more definitely and more cogently propounded by Dr Michael Foster, than by any other physiologist with whom we are acquainted. In his recent *Text Book of Physiology* he explains in the most luminous way the part which "resistance" plays in nervous phenomena[1].

[1] Whilst this paper is in the press, our attention has been called to Bernstein's *Nerven und Muskel-Systeme*, 1871. In Section IV. he arrives at very similar conclusions to those we have expressed in the paper already referred to. He says, "Physiological facts point to the conclusion that there is a connection of the sensory centres with one another," "for a phenomenon which forcibly points to such a connection, is that of irradiation. It is known that if a sensation is increased so as to become pain, it will not confine itself to the spot which has been irritated; the whole hand, nay, the whole arm, may ache, if the cause of the pain is only in a finger. It even happens that in such a case we feel the same sensation of pain in the corresponding finger of the other hand, though in a less degree. This phenomenon can only be explained by peculiar arrangements and processes in the perceiving central organs." "But it will be asked,

We were unaware till after writing our paper that this property of the cord was recognised; when, on referring to Hermann's *Physiology*, we found it mentioned there, and we adopted his expression "resistance" instead of the term "increased diffusibility" we had devised for ourselves.

Most writers consider tetanus to be due simply to increased excitability of the cord; indeed, in most works on Therapeutics it is taken for granted that tetanus is evidence of increased excitability of the cord.

Those writers who attribute tetanus simply to increased excitability of the cord imply the existence of resistance, though they do not appear to recognise the necessity for such a property. According to their view, in traumatic tetanus, and in strychnia tetanus, the reflex function of the spinal cord is greatly heightened, so that a slight irritation sets free in the cord an excessive discharge of nervous force, so strong indeed that overstepping the part of the cord functionally connected with the irritated nerve, it may spread, and excite a discharge of force throughout the cord. In other words, they believe that in health a discharge of force is restricted within certain areas of the cord producing co-ordinated action, but in an excited tetanic cord, the resistance limiting the discharge to certain areas is overcome, and the stimulation radiates throughout the reflex portion of the nervous system. This view, therefore, whilst implying a resistance or limiting force, in the central nervous system, possible however to be overcome, implies that this resistance is a constant force incapable of being heightened or depressed by disease or medicines.

Our observations in the paper previously referred to, show that in the tetanus induced by Buxus Sempervirens, and by Gelseminum, the diminution or destruction of the resistance

why do only strong impressions cause irradiation, and why not also weak ones? and then, why does not irradiation extend over the whole sensory centre; whereas it occupies only part of it? We are hereby led to an assumption which we shall render probable also by other reasons; namely, that the excitation has to overcome resistance in the ganglionic cells, and, on account of it, undergoes a loss in its intensity." Not only may impressions radiate in sensory centres, but "it also happens that the pain may cause reflex cramps. Then the stimulus is so great that in spreading out through the neighbouring sensory centres it is not yet reduced to its liminal value, and it then enters motor centres, first of all such as are situated on the same level with the irritated sensory centres and the spinal cord." Speaking of strychnia tetanus, he says, "It is simply due to a depression of this resistance in the nervous centres."

is the sole cause of the tetanus. To make ourselves clear we draw attention to the fact that both box and gelseminum are powerful depressors of the reflex function of the spinal cord, and that in full doses they soon produce complete paralysis of the cord.

In a frog poisoned by either drug we get first great weakness; the animal hops with difficulty, or perhaps can barely crawl, effects due to the action of the poison on the spinal cord, then tetanus supervenes. But the tetanic paroxysms, though very distinct, are in many instances slight. At one period we can get either a normal co-ordinated action or tetanus, according to the degree of stimulation, a weak stimulus producing a co-ordinated reflex act, a stronger stimulus, tetanus. At this time, as the tetanus grows stronger, the normal co-ordinated reflex action is growing weaker; and after a short time, tetanus also grows weaker, and ultimately slowly declines, till at last it is expressed only by slight quivering in all the muscles of the body. Now here we maintain that at the onset of the tetanus there is no increased excitability of the cord, but the very reverse state—paralysis: for the tetanus is preceded by paralysis of the cord. As the tetanus becomes more marked, normal co-ordinated action grows less, shewing that paralysis of the cord is progressing; and at last tetanus itself becomes excessively feeble, shewing that the cord is almost exhausted and paralysed. If then we have no increased excitability, how does it happen that an impression, say to the tip of one toe, after reaching the cord is not restricted to its proper portion of the cord, but diffuses itself throughout it, causing a general, but weak, evolution of nervous force, and consequently a weak, but general, contraction of the muscles, that is to say, tetanus? This can be only explained on the supposition that some change has taken place in the cord, whereby a stimulus is no longer confined to a part of the cord, but can diffuse itself; that some restraining or localizing influence is reduced or destroyed, and to this is given the name "resistance."

Further, we found that in brainless frogs after two or more days, when reflex action had begun to decline, on striking the animal between the shoulders we induced tetanus, and as co-ordinated reflex action grew weaker, the tetanus meanwhile

became stronger, and was more easily induced; and in some cases, a few hours before the cessation of reflex action we excited strong tetanus lasting half a minute to a minute, the animal becoming rigid from the powerful muscular contractions. Now we submit that in these cases the tetanus could not be due to increased excitability, unless it is maintained that the operation excited inflammation of the meninges of the cord, a supposition highly improbable, for various reasons. We maintain that the tetanus is due to diminution of the resistance in the dying cord, enabling a powerful stimulus, as a blow on the trunk, to spread throughout the cord, and produce tetanus. For further details we must refer the reader to the paper we have mentioned.

We now record some additional observations we have lately made. These we think conclusively prove that tetanus is not always due to increased excitability of the cord. These observations, too, constrain us to admit a resistive power susceptible of modification, the other functions of the cord remaining but little or not at all affected. We pithed[1] and destroyed the brain of three frogs, and then watched for the decline of reflex action. On the third day this was much weaker; in one frog so weak that, on pinching a toe, it only feebly withdrew its legs. We then injected under the skin of the back $\frac{1}{1500}$ grain of strychnia, which in about half an hour induced tetanus. This was very weak in the frog whose reflex action was nearly annulled, and the tetanus in this instance, though distinct, was feebler than the amount of muscular force developed in a normal vigorous reflex act; in other words, the reflex act, though tetanic, was weak.

In the other two frogs, with reflex power much less weak before the injection, we induced strong tetanic convulsions on the slightest irritation, or even shaking the table, the paroxysms lasting a minute or longer. Next day, however, the tetanus was much weaker, and about equal to the tetanus induced by strychnia in the frog with very weak reflex power. The tetanus grew weaker and weaker, but persisted till all reflex action became extinct; and for some time before this, the muscular

[1] Perhaps it is hardly necessary to say that by the term pithed we mean division of the cord opposite the occipito-atlantal membrane.

force displayed after stimulation was far less marked than that occurring in a normal co-ordinated reflex act. We again had weak tetanus excited in a weak and dying cord. These experiments we several times repeated.

Now we venture to maintain that it is impossible to explain this tetanus otherwise than on the supposition of a resistive force, which the strychnia weakened or destroyed. It certainly cannot be explained on the supposition that strychnia simply produces increased excitability of the cord. We are not now denying that strychnia may "excite" or "stimulate" the cord, but admitting this, the tetanus we have just described cannot be due merely to this increased excitability; for were this so, the strychnia should have first improved, then completely restored normal co-ordinated reflex action, and then, on the cord becoming still more "stimulated," tetanus ought to have supervened.

It may be objected that with brainless frogs in a few hours or in two or three days the afferent and efferent nerves become depressed as well as the spinal cord; and hence, though strychnia may restore the lost functional activity to the cord, yet as the impression conveyed thereto is weakened, and the conductivity of the motor nerves is also depressed, the tetanus itself ought to be very weak. We therefore devised the following experiment:—We pithed and pegged a frog, and after tying the femoral vessels of the right leg close to the trunk, we injected into the abdominal cavity a mixture containing one grain of extract of Calabar bean, and $\frac{1}{120}$ grain of strychnia. The Calabar bean we used to depress the cord, and as we wished to induce depression of the cord without effecting any alteration in the afferent or efferent nerves, we tied the vessels of the right leg, thus protecting the tissues below the ligature from the effect of the drug. In twelve minutes slight tetanus set in, the legs on strong mechanical irritation being powerfully shot out once, and once only, after each stimulation. Co-ordinated and tetanic reflex action persisted simultaneously; that is, a weak stimulus excited co-ordinated action, a stronger, the tetanic extension of the legs just described. The co-ordinated reflex action grew weaker and weaker, the tetanus at first remaining undiminished, then it also declined. In this

experiment the action of the Calabar bean at once reduced the cord to the same condition as in a frog which has been pithed two or three days, but of course without depressing either the afferent or efferent nerves of the ligatured leg.

Our argument is otherwise strikingly supported. In brainless frogs (frogs pithed and pegged) reflex action often declines much more quickly in one hind leg than in the other. To a moderate sized frog with very unequal power in the hind legs, one leg being rather vigorously withdrawn on irritating its toes, whilst the other was only partly withdrawn, we injected under the skin of the back $\frac{1}{1500}$ grain of sulphate of strychnia. In half an hour slight tetanus set in, first in the weaker leg, being for some time decidedly stronger in this leg. Now if strychnia tetanus is simply due to "stimulation," in other words to increased excitability of the cord, then the tetanus should certainly have first shown itself in the stronger leg, as it would naturally require less stimulation to induce tetanus in this than in the weaker limb. We noticed also that at a time when the tetanus was so slight that we doubted if it were present, by exercising the limbs and thus weakening co-ordinated action we induced decided tetanus, which rest again weakened, at the same time strengthening co-ordinated action, and strong tetanus could be again induced by a second time weakening the cord by exercising the limb. Now were strychnia tetanus due simply to "stimulation" (increased excitability), it is obvious that the very reverse should have happened.

A similar fact is often witnessed in disease, when paralysed limbs sooner become tetanized by strychnia than other parts of the body, as in the case of hemiplegia from brain disease. Here half the cord is not exercised at all or but slightly, and consequently its nutrition becomes defective, and it wastes. Strychnia will induce tetanus more readily in this depressed half of the cord than in the opposite healthy half.

But it may be said we admit a resistive force which may be overcome, and as the cord dies—as the reflex function diminishes—this resistance will *pari passu* decline; so that with a slight improvement of the reflex function, the evolution of nervous force in one part of the cord will overpower the weakened resistance, and spread throughout the cord. This position

concedes at once that the resistance is alterable in amount, thus admitting a part of our contention. But the explanation in question is altogether inadequate to explain the very different effects of paralysers of the cord. Thus to compare three drugs —Physostigma, Gelseminum, and Box: Physostigma paralyses the cord without producing tetanus; Gelseminum paralyses the cord, and produces weak tetanus; Box paralyses the cord, and excites strong tetanus. How are we to interpret these different effects? Why do Box and Gelseminum tetanize, and not Physostigma? Why should Box tetanize far more than Gelseminum? Before attempting to explain this apparent anomaly, we must interpose two preliminary considerations:—

1. That tetanus is producible only in two ways, either by increasing the excitability of the reflex function, so that the evolution of force may be sufficient to overcome the normal "resistance," and spread throughout the cord; or the "resistance" itself being diminished, an impression conducted to a cord with its reflex function in a normal or even in a depressed state, can overcome the weakened resistance, and affect the whole reflex portion of the cord.

2. It is quite inconceivable that a drug should simultaneously both depress and stimulate (increase excitability of) the same function.

Now, Gelseminum and Box, whilst they both tetanize the cord, depress at the same time the reflex function, and consequently cannot possibly produce tetanus by "stimulating" the cord. Their tetanizing action therefore can be explained solely by their power to diminish "resistance." The difference in the amount of tetanus, produced respectively by Gelseminum and Box, we explain by inferring, that Gelseminum which induces considerable cord paralysis with weak tetanus, exerts a greater effect on the "resistance" than on the reflex function, and the difference being but slight, we get weak tetanus. Box produces cord depression with much stronger tetanus, showing that the drug exerts an effect far greater on the resistance than on the reflex function; and the resistance being greatly weakened before the reflex function is much

depressed, tetanus excited by Box is far stronger than that from Gelseminum.

Granting therefore that whatever depresses the cord will diminish resistance, we must admit, that some remedies manifest a greater power over resistance than over the reflex function; and when the depression of resistance is greater than the depression of reflex action, we get tetanus. The relative effect on the reflex and the resistive functions well explain the various degrees of paralysis associated with tetanus, and the strength or weakness of the tetanus itself.

We would suggest that conceivably we may have four combinations in tetanus.

1. Tetanus with increased excitability and normal resistance of the cord.

2. Tetanus with increased excitability, and diminished or destroyed resistance of the cord.

3. Tetanus from mere diminution of resistance.

4. Tetanus with depression of the reflex function and diminished resistance.

We have adduced in this paper sufficient evidence of the fourth form of tetanus, and have elsewhere expressed a doubt if the first and second kinds of tetanus ever occur.

Surely, it will be said, the strong tetanus of strychnia must be due to increased excitability of the cord, as well as diminution of resistance; for in a paroxysm, induced by even a slight irritation, the amount of muscular force, and *ergo* of the nervous force developed in the cord, is far greater than occurs in a normal co-ordinated reflex act, and this excessive evolution of force proves the increased excitability of the cord. But we think that strychnia tetanus is best explained by simply temporary diminution or abolition of resistance. For we have shown in the pamphlet already referred to, that loss of resistance, even with depression of the reflex function, will produce strong tetanus. This is the case with Box. This drug, as we have seen, produces first partial cord paralysis; then strong tetanus ensues, whilst the co-ordinated reflex contractions, which can be induced by weak stimulation, are at the same time

growing progressively weaker; that is to say, we get strong tetanus with progressive cord paralysis.

In order to explain these strong paroxysms when the evolution of nerve force is far greater than that occurring in a normal co-ordinated act, it is obvious we must assume that the resistance not only restricts impressions to certain areas of the cord, but that it also limits the amount of force evolved; in fact, by paralysing "resistance" we not only allow a stimulus to spread throughout the reflex portion of the cord, but also to set free an increased amount of nervous force from every portion of the cord and motor parts of the brain. In other words, the function or condition to which the name "resistance" is given not only localises but restrains reflex action in the spinal cord. If then, in the case of Box, we get strong tetanus with slight depression of the cord, we think it possible that the still stronger tetanus of strychnia may be due simply to depression of this resistive function without any increased excitability. Hence, as in the case of Box, but in even greater degree, a slight stimulation not only spreads throughout the cord, but sets free an excessive amount of nervous force.

It will probably be objected that if diminution of resistance permits also the evolution of an excessive amount of force—that resistance in fact not only localises but restrains or controls the amount of reflex action—then, as resistance becomes weakened, the co-ordinated reflex acts should become stronger; as in that stage of Box and Gelseminum poisoning, when, according to the strength of the irritation, we obtain either a co-ordinated or a tetanic reflex act, the co-ordinated act should become stronger. This is not true of Box and Gelseminum poisoning, probably because, as the tetanus sets in and grows more severe, the paralysis of the cord progresses quickly, so that any increase in normal co-ordinated action due to diminution of resistance would escape detection; though we must grant that this paralysis should likewise weaken the tetanic reflex act. In strychnia poisoning, where there certainly is no weakening of reflex action, the co-ordinated reflex acts on the onset of tetanus do become stronger, as the following observation repeated several times establishes. We pithed and pegged a frog, and when reflex action had considerably declined, but the

limbs were still withdrawn under the stimulus of pinching or electricity, we suspended the brainless animal, by passing a pin through the lips, and pinning it to a retort holder, so that it hung with its legs suspended, and then injected $\frac{1}{1500}$ grain under the skin of the back, and watched for the onset of tetanus. With this small dose tetanus came on slowly, remaining for a long time comparatively weak, so that a slight irritation induced a co-ordinated reflex act; a stronger one, tetanus. In this stage we found that co-ordinated reflex action was much more easily and powerfully induced than before tetanus set in. Thus, before the injection of the strychnia only the irritated leg was withdrawn, and once only, and then again relaxed; but after the setting in of tetanus the leg, in a co-ordinated act, was first withdrawn on slighter irritation; next, as tetanus increased, both legs were withdrawn; and later, both were withdrawn and extended several times, with even a very slight stimulus, as, for instance, the very slightest touch. This effect of strychnia was still better exemplified by the following experiment. A frog, pithed and pegged seventy-one hours beforehand, we suspended by a pin passed through the lips and fixed to a stand, on each side the right ankle we placed the thin wires of the electrodes, tying them to the ankle by waxed thread, then by means of Du Bois Reymond's induction coil we ascertained the weakest current capable of exciting a reflex act. Then we injected $\frac{1}{1500}$ gr. of strychnia under the skin of the back, the instrument standing at 10·5, and as tetanus gradually set in a weaker current was sufficient to produce a co-ordinated reflex act. Thirty-four minutes after the injection, reflex action was induced with the coil standing at 11; in an hour, at 12; in an hour and twenty minutes, at 13; in an hour and a half, at 14; in an hour and forty minutes, at 16. Surely this, an objector might say, is increased excitability of the cord. Of course strychnia so affects the cord that a slight stimulus evokes a very great discharge of nervous force; but the question we raise is this:—Does this increased evolution of nervous force depend on some alteration in the composition of the cord elements, so that chemical changes and consequently the production of force are more easily induced; or is this increase

of force due to weakening or destruction of some controlling power which has been termed "resistance"?

In support of the theory of resistance, we must again refer to the effect of Box on the cord. This drug first produces cord paralysis, and whilst this quickly advances, strong tetanus occurs, which, as we have said, cannot be due to increased excitability, but must, we think, depend on loss of "resistance" of the cord; and we suggest that it is at least feasible that even the strong tetanus of strychnia may depend simply on loss of resistance, though as the reflex function is in no degree weakened, this tetanus is more powerful than that of Box.

We here adduce some observations confirmatory of this view.

In a brainless frog, after three or four days, reflex action so far declines that it cannot be excited in the smallest degree by stimulation of the extremities; but a sharpish blow over the spine produces slight and general muscular contraction. On repeating the blows, the muscular contraction grows stronger and stronger, at last becoming decidedly tetanic; and now if the blows are still continued, the muscular movements become abolished. These effects we explain in the following way:— The blow on the back diminishes the "resistance" at first very slightly, and though all the muscles are affected they contract but slightly; a repetition of the blows, of the same strength, reduces the resistance more and more, and with each blow a greater amount of nerve force is evoked; that is, the amount of stimulation remaining the same we produce a far greater amount of muscular contraction. Repeating the blows still further, we depress the cord, and at last abolish all reflex action. The increased evolution of nervous force in the cord can be explained, we think, only by the fact of diminished resistance. The augmented evolution of nervous force cannot be due to excitement of the cord, since in this experiment there is nothing to suggest or to explain the increased excitability, and, as we have said, we took care that the blows should be as nearly as possible of the same strength. If this explanation be accepted, then it shows that through diminution of resistance a greater force is evolved with the repetition of a stimulus always of the same strength.

Now if we give a dose of strychnia to a frog in the condition just described, in a short time, when absorption has taken place, we bring the cord of that animal to the condition of the frog which has undergone a repetition of blows on the back; that is to say, one blow will produce a decided, though weak, tetanic contraction. Here the strychnia acts like the repeated blows, weakening resistance, so that a stimulus will evoke a greater amount of nerve force than would have occurred before the resistance was depressed.