BRITISH MEDICAL JOURNAL

LONDON

SATURDAY MAY 15 1943

NERVE REGENERATION

In addition to its intrinsic interest, the subject of nerve regeneration becomes increasingly important in time of war, and it is good to know that British workers are to the fore in attempts to solve the numerous theoretical and practical problems that arise in connexion with it. There is an extensive literature on the subject, as many as 928 papers being collected by Rossi and Gestaldi[1] up to 1934. Most of these lay emphasis on regeneration from the point of view of histology or function, but few studies have combined the two. In a recent review Young[2] has pointed out that the functional recovery of a regenerated nerve becomes complete only when the fibres are of a certain diameter and state of medullation, and can carry impulses of appropriate frequency and velocity. On this premise Holmes and Young[3] put forward six factors which may affect the success of secondary nerve sutures: (1) The first is the power of the central stump to send out new fibres. They find that this power is not affected when the axons are cut twice, either within a few days or nearly a year after the original injury. (2) The second is the power of the stumps to unite. This depends upon the outgrowth of Schwann cells from the peripheral stump. This outgrowth is at a maximum about two to three weeks after section of the nerve. There is evidence that union made after this interval is somewhat more successful than after primary suture. From about 100 days onwards the power of union declines, and long delays of union are less likely to succeed than primary suture. (3) The total diameter of the peripheral stump shrinks in the later stages of degeneration, sometimes by as much as a half. This fact makes a good suture difficult to effect and militates against the successful re-entry of fibres into the peripheral stump. (4) The shrinkage of the lumen of the Schwann tubes results in fewer fibres entering each one, and this in turn diminishes the chance of successful re-connexion. (5) After delayed suture, medullation is delayed in the peripheral stump and the fibres remain of small diameter for much longer than after primary suture. (6) The factor of re-innervation of end-organs is of great importance. Holmes and Young conclude that the process of the union of stumps and the regeneration of a new functionally efficient stretch of nerve are less satisfactory after the longer period of degeneration. Postponement of suture for one or two months does not prejudice the chances of recovery and may even improve them. Longer delays, especially those greater than six months, bring about conditions which are likely at least to retard recovery and may permanently prevent it.

Weddell[4] has correlated both the macroscopical and microscopical appearance of regenerating nerve fibres with the diminution of the area of sensory loss following interruption of nerve in the rabbit's ear. He finds that nerve fibres first advance along the original main nerve fasciculi. The first fasciculi to be re-innervated are those lying in closest proximity to normal nerve trunks. He has also found that cutaneous nerve bundles close to the larger blood vessels are more rapidly re-innervated than those further away. This, it should be emphasized, is distinct from the extension of adjacent normal fibres which also occurs towards the area of sensory loss. When the nerve trunks have become re-innervated the fibres pursue a tortuous course through the cutaneous plexus towards the skin surface. The finest visible endings of the nerve fibres are associated with Schwann cell pathways, which retain the pattern of the cutaneous plexus in the normal ear. On no occasion in the rabbit's ear has the tip of a regenerating nerve fibre in the cutaneous nerve plexus been seen pursuing a course independently of a Schwann band.

In a recent publication Weddell[5] observed that cutaneous sensory spots are each innervated by multiple nerve fibres. He suggests, therefore, that during the course of regeneration these will arrive at each separate spot at different times because they approach it from different directions, and the ultimate courses followed by the individual fibres will necessarily be of different lengths. Thus there will be a phase during regeneration in which each sensory spot is innervated by a single fibre instead of by multiple fibres. Such a stage in regeneration has now been found to occur, and hence the physiological findings of Trotter and Davies[6] are seen to have an anatomical basis—that is, if the process of regeneration of cutaneous nerve fibres in the ear of the rabbit can be assumed to be similar to that in man. The more rapid regeneration of nerve fibres along blood vessels is also in accord with the observations of Trotter and Davies, who observed that vasomotor control returned more rapidly than skin sensation. These phenomena evidently play some part in the process of diminution of areas of sensory loss which are observed clinically to take place from the periphery towards the centre of a degenerated area rather than from the centre outwards. In contrast with this mode of innervation the return of skin sensibility in regions not surrounded by areas innervated with normal nerves, such as the digits, is by an advancing wave of sensory recovery along the line of the cutaneous nerves supplying the skin. A similar phenomenon occurs in the rabbit's ear after complete denervation. The more rapid regeneration of cutaneous nerve fibres in the neighbourhood of blood vessels may serve to explain the bridges of cutaneous sensibility which are commonly found, in man, to cross an area of sensory loss during the course of regeneration from the proximal stump of the divided nerve.

The process of nerve regeneration throughout an area of skin involves first the rapid regeneration of nerve fibres along the main subcutaneous nerve trunks, and it is only at a later date that fibres extend from these trunks towards the skin by way of cutaneous nerve plexuses. In other words, regenerating nerve fibres ramify in the subcutaneous tissues some time before they give extensions to the skin itself. This is important from the point of view of nociceptive sensory tests which are used to determine the progress of sensory recovery. For instance, it has been found in clinical cases that "deep pricks" (2 to 3 mm. deep) will arouse pain in an area which is still anaesthetic to lighter pricks (1/2 to 1 mm. deep). This furnishes an explanation for the statement that one of the earliest indications of recovery of skin sensibility is pain caused by pinching the skin, for this manipulation necessarily includes the subcutaneous tissues. The importance of using standard instruments, which will give approximately constant stimuli from day to day in the same patient, cannot be overemphasized if a true picture of the course of sensory recovery (nociceptive) is to be obtained.

1 *Rev. Path. Nerv.*, 1943, **43**, 1.
2 *Physiol. Rev.*, 1942, **22**, 318.
3 *J. Anat.*, Lond., 1942, **77**, 63.
4 Ibid., p. 49.
5 *Proc. roy. Soc. Med.*, 1941, **34**, 776.
6 *J. Physiol.*, 1909, **38**, 134.

The work reviewed above has demonstrated the process of peripheral nerve regeneration in detail and has accounted in some measure for the clinical observations made on functional recovery. After complete division of a nerve early suture is important. In cases of incomplete division or neurapraxia (Seddon[7]) a most careful assessment of the damage done is essential before operative intervention is decided upon. To this end Guttman[8] has shown the value of the thermoregulatory sweating test, which gives a clear indication of the amount of autonomic damage in the cutaneous nerve. More recently Weddell, Feinstein, and Pattle[9] have shown that an accurate assessment of the injury to a peripheral nerve supplying a voluntary muscle can be made by electromyography. It is to be hoped that by combining these two procedures with a clinical examination the treatment and prognosis of peripheral nerve injuries will advance considerably.

To complete the picture of work in progress on nerve regeneration we will refer briefly to the less familiar problem of fibres in the central nervous system—a matter recently investigated by Le Gros Clark.[10] In 1910 Tello[11] implanted fragments of peripheral nerves in the brain. He claimed that regenerating fibres were seen in the graft, and in some sections could be seen penetrating the perineurium from the tissues of the host brain. Tello concluded that the Schwann cells were a source of a specific neurotropic substance which attracted fibres from cerebral neurones to grow towards them. Le Gros Clark, on the other hand, found a few regenerating fibres within his implanted graft in only 3 out of 13 experimental animals. In two cases regenerating nerve fibres were traced to a fasciculus accompanying newly formed blood vessels which approached the graft from the tissues of the host brain. In one case regenerating fibres within the grafted nerve fragment appeared to have entered the latter from the tissues at the surface of the brain. In no instance could regenerating fibres be traced into continuity with the fibres of the host brain, though the possibility of such a derivation could not be excluded. In some experiments many fibres of the surrounding white matter were disposed in fasciculi orientated towards the graft. This appearance was due partly to traction in the host tissue by the graft and partly to the dislocation of pre-existing fibres by a cellular infiltration. In two experiments spinal ganglia grafted into the brain showed great regenerative activity. Many fibres were found to penetrate into a zone of cellular infiltration separating the graft from the tissues of the host brain. However, no regenerating fibres from the host brain were found to extend into this zone towards the graft. It is concluded from these careful and detailed observations that the intrinsic fibres of the host brain have little if any regenerative capacity compared with peripheral nerves.

Sugar and Gerard[12] reported evidence of regeneration after section of the spinal cord in foetal and newborn rats. However, it is well recognized that the central nervous system of the newborn rat is very immature, and the post-operative growth of nerve fibres may well have been due to the developmental outgrowth of axons which would be proceeding normally at this time. These authors also cut through the spinal cord in young rats aged 3 to 5 weeks and in some cases reported regeneration across the scar. But, as is pointed out by Le Gros Clark, the anatomical evidence for this is not easy to assess; the consistency of the white matter of the central nervous system makes it difficult to produce clean lesions experimentally, and the fibres which appear to cross the scar at the site of lesion may be the frayed ends of the pre-existing fibre bundles pulled out of their normal position and left overlying the line of the knife cut. In addition to this the central nervous system of young rats even a few weeks old is relatively immature. Mitoses in the spinal cord reach their height in white rats about the 7th day after birth. It seems probable, therefore, that axons within the central nervous system do not regenerate once they are mature. It is also clear that the explanation for this is not to be sought in the absence of Schwann cells in the central nervous system but in other factors. Tower[13] has lately shown that the anterior horn cells in the spinal cord, when avulsed, can send out new axons along paths devoid of Schwann cells. There seems to be some factor related to all peripheral nerves which is absent in the intrinsic neurons of the central nervous system.

[7] *British Medical Journal*, 1942, **2**, 237.
[8] *J. Neurol. Psychiat.*, 1940, **3**, 197.
[9] *Lancet*, 1943, **1**, 236.
[10] *J. Anat.*, Lond., 1942, **77**, 20.
[11] *Trab. Lab. Invest. biol. Univ.*, Madrid ,1911 **9**, 123.
[12] *J. Neurophysiol.*, 1940, **3**, 1.

RESPONSIBILITY OF A PSYCHOPATH

The shortcomings of the "rules in M'Naghten's case" were again demonstrated in a recent trial for murder at the Old Bailey (Rex *v.* Lees-Smith). The defence alleged that the accused's act had been due to mental deficiency. Lengthy medical evidence was given concerning a number of laboratory tests which were applied to the prisoner. The witnesses found, in short, that he suffered from a congenital constitutional defect of development, manifesting itself as emotional immaturity, poor physique, and minor abnormalities of the central nervous system. He did not necessarily suffer from epilepsy, and in their opinion he suffered rather from psychopathic personality. They gave evidence that when his blood sugar was low and he overbreathed a change occurred in his brain whereby his judgment was impaired and his full perception of events was distorted. Before committing the crime of matricide he had drunk four pints of beer. A similar quantity given in the laboratory had the effect of lowering his blood sugar and aggravating his abnormality. The medical witnesses concluded, in terms of the M'Naghten rules, that when he killed his mother he knew what he was doing and that it was wrong, but his brain was functioning abnormally so that he was unable fully to appreciate the nature of his act.

The learned judge explained clearly to the jury the meaning of the M'Naghten rules, but in spite of his direction they found the prisoner guilty but insane. Everyone concerned with the case realized that the prisoner would almost certainly have been reprieved on the advice of the Home Secretary. The defect of the M'Naghten rules, which are now just 100 years old, is that they do not provide for the criminal who knows what he is doing and knows that it is illegal but, owing to a diseased or defective mind, cannot restrain himself from doing it. Many murderers have in fact been hanged in spite of strong evidence that their mental state had deprived them of self-restraint, and perhaps as many have been found guilty but insane in face of the M'Naghten rules. These rules were laid down by the common-law judges in 1843, and knowledge of human psychology has much advanced in the last hundred years. In 1924 Lord Darling introduced into the House of Lords a Bill to provide for the defence of "irresistible impulse," but it was opposed by several Law Lords and its mover withdrew it. The general feeling among lawyers seems to be that many criminals who richly deserve death would be able to persuade a jury that they had acted under an irresistible impulse. Persons who feel in this way perhaps underrate the capacity of juries to assess the medical evidence wisely and to reject a plea of this kind if the accused does not clearly show that his mental abnormality

[13] *Arch. Neurol. Psychiat.*, Chicago, 1943, **49**, 1.