CHANGES IN HUMAN VOLUNTARY MUSCLE IN DENERVATION AND RE-INNervation

BY

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A study of the changes in human voluntary muscle during denervation and re-innervation is essential for a proper understanding of lower motor neurone lesions, especially peripheral nerve injuries. There are significant changes in structure and physiological properties. The subject will be considered from the point of view of histology, electrical reactions, electromyography, and treatment of paralysed muscles.

Structural Changes

For the sake of clarity some of the characteristics of a normal muscle must be mentioned first. A voluntary muscle is composed of numerous fasciculi made up of cross-striated fibres arranged in compact parallel bundles. The nuclei are for the most part arranged at the periphery of the fibres. Some preparations show minute granules regularly spaced at the level of the dark bands. The nerve fibres can be clearly seen, and the axons are myelinated to the point where they enter the motor end-plates. A single nerve-cell, its axon, and the muscle fibres innervated by it constitute the motor unit. The branching of the axon occurs close to the point of entry into the muscle. The blood supply is plentiful, for the capillary network is rich. All these structures are supported in delicate and sparse connective tissues.

In the early stages (one to three months after denervation) there is a loosening of the compact arrangement of the fibres, an apparent numerical increase of the nuclei, and little change in the connective tissue. The blood vessels appear to be dilated, indicating stasis of the circulation. The nerve fibres undergo Wallerian degeneration, and when all the debris of the disintegrating fibres has been removed the empty Schwann tubes remain and can be traced to the empty motor end-plates.

From three months onwards there is a progressive shrinkage of the muscle fibres, cross-striation fades from the earliest days, and the granules become increasingly apparent and irregularly arranged. The vessel walls thicken and some are completely blocked. There is an increase of connective tissue, apparently beginning around the vessels and spreading throughout the muscle, invading and finally obliterating the terminal Schwann tubes and motor end-plates. As the muscle fibres atrophy they are replaced by fat and connective tissue. Ghosts of fibres, a few capillaries, and the larger nerve trunks may be seen surrounded by fibrous tissue, and finally the muscle may resemble tendon, or there may be a few scattered connective-tissue tubes containing granules—all that remains of the muscle fibre.

The time course of these changes is of great importance, for upon the reversibility of the changes in the muscle fibres depends the recovery of function. The changes are predominantly those of atrophy and not degeneration. Fibrous tissue seems to wage a war of attrition upon muscle fibres. Up to one year after denervation it is possible to expect a fairly good degree of functional recovery; from then onwards the prognosis deteriorates, and as a rule from three years onwards the prospects are exceedingly poor. The fibres are atrophic and have lost their characteristic structure; connective tissue is strangling and obliterating the contractile tissue, vessels and empty motor end-plates, and Schwann tubes. There are exceptions to this statement, for there are notable individual variations: sepsis, age, mobility of the limb, and physiotherapy influence the rapidity of the changes.

The nature of the lesion in the nerve influences the degree of functional recovery profoundly, as this determines the number and maturity of the axons which ultimately reach the end-organs. In axonotmesis (Seddon, 1942, 1943); Gutmann and Sanders, 1943) the supporting tissues of the nerve at the site of the lesion are intact, although the trauma has been sufficient to cause complete peripheral degeneration of the

axons. There is minimal intraneural scarring, and regeneration of the fibres occurs spontaneously and without obstruction down the original pathways. The time of denervation depends almost entirely upon the level of the lesion above the muscles (Gutmann, Guttmann, Medawar, and Young, 1942; Seddon, Medawar, and Smith, 1943). The motor end-plate is intact, cross-striation is visible, and atrophy of the fibres is slight. Good powerful independent muscle action is restored in such cases and there is an apparent complete reversal of the atrophic changes in the muscle although the pattern of innervation is slightly abnormal. Where the nerve has been more seriously damaged there may be partial disruption of the Schwann tubes and scar formation. Here some nerve fibres will be obstructed and there will not be an even advance of regenerating axons. Some permanent weakness and atrophy may be expected and there may be impairment of independent action of the muscles.

In complete division of the nerve no recovery can take place without surgical intervention. There is inevitable delay in re-innervation: at the site of the suture scar tissue is present in varying degrees. Moreover, there is unavoidable confusion of the axons at the suture line; therefore regeneration cannot take place down the original Schwann tubes. Some axons from the central stump may never penetrate the scar, others may escape laterally, and those that reach the peripheral stump may enter abnormal channels. The number of nerve fibres reaching the end-organs is diminished. If the muscle has been denervated for some considerable time the finer Schwann tubes are blocked and the motor end-plates will have disappeared. The regenerating nerve fibres may escape from the Schwann tubes, and they run for long distances between and across the muscle fibres seeking to make new connexions; some fail completely, and are therefore wasted (Gutmann and Young, 1944; Bowden and Gutmann, 1944). The reversal of changes in muscle fibres is hampered by the time of denervation and by incomplete and sometimes incorrect re-innervation. Full power and independent action can never be restored. Where delay has been too great the muscle may be incapable of recovery and the best degree of re-innervation will be of no avail (Bowden and Gutmann, 1944).

Electrical Reactions

Associated with the structural changes there are certain important changes in the function of the denervated muscle. Loss of tone and voluntary and reflex action is immediate and there is a more gradual change in electrical excitability. Each tissue has a characteristic excitability. Some are quick tissues—that is, they respond to electrical stimuli of low intensity and short duration: nerve is an example of such a tissue. Others are slow—that is, they will respond to stimuli of short duration only if the intensity is great.

A normal muscle responds to percutaneous faradic stimulation at low intensities; this stimulus is of short duration. The muscle contracts because it is receiving impulses via the intramuscular nerve twigs. As the nerve degenerates its excitability decreases and is ultimately lost. At the same time the muscle is losing the power of responding to faradic stimulation. The muscle fibres themselves are being stimulated, and the faradic response either disappears or is obtained only with a high current; the galvanic response, however, is much more easily elicited and the contraction becomes sluggish. This quantitative and qualitative change was described by Erb (1876) as the reaction of degeneration (but, as we have seen, the early changes in the muscle fibres do not merit description as degenerative). The sluggishness of the galvanic response is possibly due to the stimulus being conducted by muscle fibres and not by nerve; the rate of conduction in muscle is slower and all the fibres cannot contract simultaneously. During denervation the threshold to galvanic stimuli rises with loss of contractile substance and may finally disappear altogether if atrophy is advanced. The failure to elicit a galvanic response in the absence of oedema indicates serious atrophic change in a muscle. During re-innervation there are changes in excitability as the nervous element reappears, but it is possible for there to be a good functional recovery while the electrical reactions are still abnormal. (Reports of a further clinical survey will be published in due course.)

Electromyography

There is another interesting alteration in electrical activity which is of great significance in diagnosis; but, unlike electrical reactions, it can be of considerable prognostic importance. The action currents of contracting muscles can be recorded—the electrocardiogram is a well-known example. By electromyography it is possible to record the action currents in a voluntary muscle.

For about 12 to 28 days after denervation there is no recordable electrical activity in human muscle on attempted movement or at rest. From 12 to 28 days after denervation fibrillation occurs: this is shown by rhythmic fine spikes totally unrelated to attempted voluntary contraction. The exposed surface of such a muscle if observed by reflected light will show numerous small scattered twitches. Fibrillation persists as long as any contractile denervated fibres remain, or until re-innervation is taking place, but in the early stages of re-innervation a muscle which has previously shown vigorous fibrillation becomes silent. Motor-unit action potentials may precede recovery of voluntary function by as much as three months, and an isolated observation of this sort is no guarantee that further re-innervation is going to occur.

The finding of both fibrillation and motor-unit action potentials indicates a partial or recovering degenerative lesion of the lower motor neurone (Weddell, Feinstein, and Pattle, 1943, 1944; Bowden, unpublished).

Treatment

We have seen that electrical reactions and electromyography may be of help in diagnosis and to some extent in prognosis. The histological findings have shown that in the muscle itself atrophy of the muscle fibres and connective-tissue proliferation are the enemies of recovery. Surgical repair, if necessary, should be undertaken as soon as possible. There is experimental and clinical evidence that atrophy of muscle can be retarded by activity induced by adequate electrotherapy. The contraction of the muscle is essential; therefore faradic stimulation of denervated muscle is useless and a waste of time. Denervated muscle responds to galvanism, and this is therefore one method of treatment.

In a series of rabbits both the left and right tibialis anterior were denervated for the same length of time. One side was treated daily with galvanism, the other was untreated; and there was considerable difference in the naked-eye appearance of the muscles. The histological picture was even more impressive: the diameter of the treated muscle fibres is much greater than that of the untreated side and the formation of fibrous tissue is minimal (Gutmann and Guttmann, 1942, 1944). This is a most convincing proof of the value of regular adequate electrotherapy. Can this experimental finding be applied clinically?

Dr. Shirley Jackson investigated the value of galvanism in a series of cases of ulnar nerve palsies (personal communications; work in press). Volumetric measurements were made at intervals. It was seen that atrophy is most rapid in the early stages of paralysis, and that electrotherapy does not wholly prevent atrophy; it can only retard the rate. At no time was there an increase in volume of the hand in the absence of re-innervation. Therefore it is essential that electrotherapy not only should be regular and adequate but should begin as soon as possible after injury.

Connective-tissue formation is retarded by physiotherapy, but it cannot be entirely prevented. The late sequel of connective-tissue formation is contracture of the paralysed muscle. Whilst contractures can and do form in active unopposed muscles, they may occur in paralysed muscles, either early or late in the course of denervation. They can be wholly prevented by daily movements throughout the whole range of the joints of the limb. Splinting of paralysed limbs is never done to obtain immobilization unless there is a fracture or an unhealed wound; the object is to prevent overstretching and to encourage activity by compensating for the paralysis, if this is possible.

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VALUE OF SUPPLEMENTS OF VITAMIN C IN PREVENTING LACTATIONAL MASTITIS

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One theory put forward for the high incidence of lactational mastitis in an industrial Scottish town (Fulton, 1945) was that a deficiency—probably due to wartime restrictions—in some food factor, or factors, was a predisposing cause. Nixon (1941) has suggested that there is a relationship between dietary deficiencies and puerperal infections, and has cited as evidence the fact that during the last war mortality from puerperal fever in Germany was almost doubled as a result of the blockade. One of the most obvious of wartime food curtailments in this country is shortage of fresh fruits and vegetables, the chief source of vitamin C. Widdowson and Alington (1941), in studying middle-class diets, have shown that in 1935 fruit supplied ten times as much vitamin C as it did in 1941 and that the average vitamin C intake in 1935 was more than double what it was in 1941.

At the time when this experiment was begun (Dec., 1941) the following assumptions could reasonably be made.

- (1) There was a high, if not an increased, incidence of mastitis.
- (2) The incidence of mastitis appeared to be greater in the winter months (Moon and Gilbert, 1935).
- (3) Some degree of vitamin C deficiency was common. Many writers had brought forward evidence to support this view (Harris and Ray, 1935; Abbasy *et al.*, 1935; Orr, 1936; Harris *et al.*, 1936; Portnoy and Wilkinson, 1938; Harris, 1940a; Youmans, 1941).
- (4) Hypovitaminosis C was likely to have increased under wartime conditions. This has since been proved by Widdowson and Alington (1941), Harris (1942), Francis and Wormald (1942), and Widdowson and McCance (1942).
- (5) Hypovitaminosis C is more likely to occur during pregnancy and lactation. There is evidence that vitamin C requirements are increased during these periods (Harris and Abbasy, 1937; Smith, 1939; Neuweiler, 1935).
- (6) There is a seasonal fluctuation in the intake of vitamin C, as fresh fruits and vegetables are more plentiful in the summer and autumn months. Evidence of this has since been published by Harris (1942), McNee and Reid (1942), Harris and Olliver (1943), Prunty and Vass (1944), and Craig *et al.* (1944).
- (7) The time of seasonal increase in the incidence of mastitis (the winter and spring months) roughly corresponds to the period when intakes of vitamin C are lowest.
- (8) Lack of vitamin C diminishes the resistance to infection (Harris, 1937; Smith, 1939; Harris, 1940b; Youmans, 1941).

If these assumptions were accepted there seemed to be some justification for postulating that vitamin C deficiency might be responsible, at least in part, for the occurrence of mastitis. An experiment was devised to attempt to verify or disprove this hypothesis. Although, admittedly, a diet functions as a whole and deficiency of one constituent only is unlikely to occur, it was thought better to investigate the effects of varying the intake of one single factor in order to attempt to obtain a clear-cut result regarding that factor. The project was to give one group of pregnant women supplements of ascorbic acid and to compare them, especially as regards the incidence of mastitis, with a group of women, similar in other respects, who did not receive supplements.