Muscle cross-reinnervation

SIR,—In a recent communication in *Nature*, Weeds *et al.*[1] described some modifications in the subunit constituents of myosin subsequent to surgical transposition of the nerves of two functionally disparate muscles (for example, a fast-twitch, glyocolytic muscle against a slow-twitch, oxidative muscle). The evident metabolic reprogramming of the cross-reinnervated muscles led them to conclude that "It would be interesting to know if the electromyogram activity of muscles does change following cross-reinnervation" (that is, is the alien-innervated muscle activated in a fashion comparable with that of the muscle for which the nerve was normally intended?).

Obviously, few if any efforts have been made to determine the actual pattern of utilisation of cross (and self) reinnervated limb muscles. Ideally such studies require precision monitoring of electromyogram activity (by chronic indwelling electrodes) or normal and alien-innervated muscles during the repertoire of physical activities of normal and experimental animals. There are, however, several less sophisticated observations available which indicate that cross-reinnervation by functionally dissimilar nerves does lead, at least partially, to the expected changes in patterns of activity of the affected muscles. Furthermore, an exchange of functionally similar nerves apparently allows some retention of the original manner in which a muscle was utilised.

In the course of several investigations on rats, I surgically rerouted either the phrenic nerve, or hypoglossal nerve, to a denervated ipsilateral sternomastoid muscle. Several months thereafter the animals were lightly anesthetised and the function of the sternomastoid muscle was observed directly through an incision in the neck. After phrenic reinnervation the sternomastoid muscle contracted rhythmically in concert with the intact contralateral hemidiaphragm (an activity that could be enhanced by temporarily occluding the air passages). Following hypoglossal reinnervation the sternomastoid twitched intermittently in conjunction with licking motions of the tongue. The extent to which this transposition of functional activity from diaphragm to sternomastoid, or tongue to sternomastoid is operative in the fully awake animal is uncertain. Nevertheless, the appropriate circuitry and functional capacity of the phrenic and hypoglossal motorpools apparently can be diverted through a cross-nerve anastomosis to a muscle (the sternomastoid) that is not primarily responsible for breathing or licking activities.

The functional consequences of self-reinnervation, rather than cross-reinnervation, have also been answered in part by Guth and coworkers[2] who demonstrated in the rat that the recurrent laryngeal nerve, some fibres of which normally transmit efferent bursts synchronous with those of the phrenic nerve, is often capable of restoring rhythmic diaphragmatic activity subsequent to a recurrent laryngeal-phrenic nerve anastomosis

Sperry[3], in still earlier studies, emphasised that a regenerated nerve tends to retain its original reflex activity.

Thus, in spite of the disparity in muscle nerves (with respect to quality and quantity of efferents and afferents, and the differences in central circuitry) there is good reason to assume that many of the nerves used in cross-reinnervation experiments continue to elicit a gross pattern of muscle activity quite similar to that of their original musculature. It is difficult, however, to envisage a precise replication of function in most cross-reinnervated muscles because of the extreme complexity and uniqueness of each nerve, each muscle, and the myriad factors interwoven in the nerve regeneration process.

Yours faithfully,

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1 Weeds, A. G., Trentham, D. R., Kean., C. J. C., and Buller, A. J., *Nature*, **247**, 135 (1974).
2 Guth, L., Soutter, L., Frank, K., Campbell, J. B., and Lloyd, J. B., *Expl Neurol.*, **2**, 251 (1960).
3 Sperry, R. W., *Q. Rev. Biol.*, **20**, 311 (1945).

THE AUTHORS REPLY:— Dr Yellin's observations are certainly pertinent to the question posed by us, and are also in line with expectation following the pioneering work of Sperry[2] to which Dr Yellin refers. The broader problem to which our query relates, however, is whether the altered patterns of motor nerve impulses which probably reach both fast-twitch and slow-twitch mammalian skeletal muscles following cross-reinnervation are by themselves sufficient to bring about the mechanical and biochemical changes which are now known to follow altered innervation. For this to be so at least four conditions must be met.

First, it must be established that alterations in the number, and or, pattern of nerve impulses reaching a normal muscle can alter that muscle's mechanical and biochemical characteristics.

Second, it must be demonstrated that following cross-reinnervation, there is an altered pattern of motor activity in the reinnervated muscles.

Third, it must be shown that the change in activity pattern following cross-reinnervation is quantitatively correct to account for the observed mechanical and biochemical changes.

Fourth, it is also necessary to demonstrate that the observed changes in the mechanical and biochemical characteristics of cross-reinnervated muscle are the direct result of the number, and or, pattern of motor nerve impulses, and are not due to some concomitant metabolic change occurring in the motoneurone as a consequence of its altered activity.

The first point is now established beyond doubt by the original experiments of Salmons and Vrbová[3], and the later work of Streter *et al.*[4] and Al-Amood *et al.*[5]. Dr Yellin's observations add weight to the expectation that the electromyographic activity of both fast-twitch and slow-twitch muscle is altered by cross-reinnervation, but, as he implies in his letter, the satisfying of the third requirement must await the quantification of the appropriate electromyograms from conscious, unrestrained, cross-reinnervated animals.

At the present stage of knowledge, consideration of the fourth requirement can only be speculative[5,6] but it is clear that if the changes following the cross-reinnervation of mammalian fast-twitch and slow-twitch muscles are to prove entirely explicable in terms of the pattern of motor nerve impulses reaching the muscles, all four criteria listed above must be satisfied. Only then can the additional possibility of another neural (trophic) factor operating in this situation be firmly rejected.

Yours faithfully,

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1 Weeds, A. G., Trentham, D. R., Kean, C. J. C., and Buller, A. J., *Nature*, **247**, 135 (1974).
2 Sperry, R. W., *Q. Rev. Biol.*, **20**, 311 (1945).
3 Salmons, S., and Vrbová, G., *J. Physiol., Lond.*, **201**, 535 (1969).
4 Streter, F. A., Gergely, J., Salmons, S., and Romanul, F., *Nature*, **241**, 17 (1973).
5 Al-Amood, W. S., Buller, A. J., and Pope, R.. *Nature*, **244**, 225 (1973).
6 Buller, A. J., in *Modern Trends in Physiology*. (edit. by Downman, C. B. B.) (Butterworths, 1972).