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FACTORS IN FUNCTIONAL RECOVERY FOLLOWING SECTION OF THE OCULOMOTOR NERVE IN MONKEYS

BY

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Introduction

THE downward rotation of the eye-ball in primates is normally associated with a corresponding movement of the upper eyelid. After oculomotor nerve paralysis, however, the superior eyelid which formerly drooped may not descend; indeed, this eyelid may actually move up while the globe and the lid on the normal side move down. Such disjunctive movements were described in man by Gowers (1879), who attributed the absence of associated lid movements to immobility of the globe in the vertical plane. Fuchs (1893) thought the phenomenon due to spreading of impulses in the nucleus of the oculomotor nerve, and Bielschowsky (1935) suggested as the cause indiscriminate regeneration of the axis cylinders in the reunited oculomotor nerve—an explanation similar to that of Lipschitz (1906) for the abnormal movements of facial muscles in patients recovered from Bell's palsy. Ford and Woodhall (1938) have recently used similar reasoning to explain various disorders of motility and sensibility which appear in the course of regeneration of cranial, spinal and autonomic nerves in man.

Similar abnormal movements of eyelid and eye-ball have been reproduced experimentally in a chimpanzee (Bender and Fulton, 1938) and all the evidence pointed to misdirected regeneration as the cause of the dissociated palpebral

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and ocular movements. The present communication deals with corresponding experiments carried out in monkeys. In all monkeys studied, some recovery of nerve function occurred after section of the third nerve.

Procedure

The observations have been made on a series of 15 young rhesus macaques (*M. mulatta*) and one chimpanzee, in which either the oculomotor, trochlear, or both nerves were severed aseptically under amytal anæsthesia, usually with scissors; the cut ends generally became separated from one another by 2–3 mm. To secure adequate exposure a large bone flap was necessary. The dura was then incised and freely turned back so that the hemisphere could be retracted without damage to the temporal lobe. A similar exposure was made for the trochlear nerve. In a number of instances proof of regeneration was obtained by secondary resection of the regenerated nerve. Daily observations were made during the first weeks after operation.

Experimental Results

Section of oculomotor nerve.—Intracranial section of the third cranial nerve in these animals resulted in the typical ophthalmoplegia seen in man and chimpanzee, i.e. there was complete ptosis, external deviation of the eye, and maximal dilatation of the pupil. The pupil did not constrict on any form of stimulation. The only orbital movement was in a horizontal plane between the outer canthus and vertical meridian. Generally by the 5th to 7th post-operative day the ptosis and external deviation of the eye-ball lessened. A change in tone in the levator palpebræ could be seen at this time, and the “fright reaction” as described by Bender (1938) had begun to be detectable. About this period also, contractions in the levator palpebræ could be reproduced by parenteral injection of eserine and acetylcholine. In other words, after the period allowed for the nerve-endings to degenerate, the denervated levator palpebræ muscle began to show signs of sensitization to acetylcholine.

The ptosis continued to diminish and by the 25th or 28th post-operative day the palpebral fissure was more than three-quarters open; when the monkey looked down with the normal eye, the upper lid of the affected eye failed to move in unison. Indeed, neither the lid nor the globe on the affected side ever moved in conjunction with vertical (up and down) excursions of the normal eye. This failure of the lid to descend has been termed by ophthalmologists the “pseudo-Graefe sign” to differentiate it from the lid lag observed in exophthalmic goitre, known as the “Graefe sign.”

In Experiment 1, which was typical, improvement was progressive so that by the 32nd day after operation the monkey was able to adduct the affected eye slightly past the vertical meridian. On the 34th day ptosis had disappeared completely. On the 30th day not only did the lid fail to descend but actually moved upward in association with downward gaze in the sound eye. This movement of the lid appeared to be due to a contraction of the levator palpebræ. The upward movement in the lid was also noted when the monkey looked to

the side requiring the action of the fully recovered internal rectus muscle, i.e. on the 49th day. There were abnormal contractions also in the recovered internal rectus muscle. When the monkey looked down with the good eye, the affected eye turned nasally. Slight adduction was again observed when the monkey looked upward. In other words, the recovered levator palpebrae and internal rectus muscle contracted simultaneously in association with intended vertical or internal movements.

Vertical movements in the recovered eye were never encountered. This, however, did not mean that the elevators or depressors of the globe remained paralysed ; on the contrary, the absence of upward or downward movements was due to simultaneous contraction in the elevators and depressors of the eye which gave no resultant movement. When, in the eye recovering from an ophthalmoplegia, the inferior rectus muscle had been previously cut, upward movements of the globe became apparent ; that is, as soon as one of the antagonists was eliminated, the action of the other became evident.

Signs of regeneration of pupillary constrictor fibres appeared later ; the first indication was on the 49th day (decrease in the pupillary diameter). At 60 days slight constriction of the pupil in association with the lid closure reflex was evident. On the 90th day there was slight constriction in association with fixation at a near point, and after many months reaction to direct and indirect stimuli appeared. In one instance the pupil constricted when the animal looked to the side requiring the action of the internal rectus muscle. This was the only instance of participation of the pupil in the massive contraction following regeneration of the oculomotor nerve. The excursions of pupillary constrictor responses were always small. All contractions were augmented by previous eserization. The foregoing data illustrate that, whenever any one of the muscles supplied by the regenerated oculomotor nerve contracted, the rest of the recovered muscles acted simultaneously.

Further evidence that the contractions *en masse* were associated with the regenerative process was brought out in stimulation experiments ; thus faradic stimulation of the cortical eye-fields, which would produce horizontal movement in the direction requiring the action of the recovered internal rectus, was accompanied by a definite retraction of the recovered upper eyelid ; similarly, stimulation of the reunited nerve proximal to the point of section 180 days after the original section resulted in a retraction of the upper eyelid, internal rotation of the globe, and slight constriction of the pupil ; stimulation distal to the point of section produced similar but more pronounced effects. Finally, section of the reunited nerve 145 days after the primary section caused a prompt reappearance of the ophthalmoplegia and abolition of responses in this eye to electric stimulation of the cortical eye-fields (Bender and Fulton, 1938). The course of regeneration in the oculomotor nerve was not materially affected by section or stimulation of the cervical sympathetic, trigeminal, or trochlear nerves.

Cervical sympathetic.—Stimulation of the cervical sympathetic trunk after section of the oculomotor nerve caused the usual exophthalmos with secondary separation of the eyelids, pilo-erection and enlargement of the pupil,

provided the pupil was not already maximally dilated. Cutting of the cervical sympathetic trunk or its superior ganglion was followed by enophthalmos, with secondary elevation of the lower lid edge and slight drooping of the upper lid (pseudo-ptosis). Although the dilated pupil in the ophthalmoplegic eye did not become smaller immediately, section of the cervical sympathetic in these monkeys caused the diameter of the pupil to decrease in a shorter time than in those in which only the oculomotor nerve had been cut. The pupil, after sympathetic denervation, dilated with intravenous or intramuscular injections of adrenaline (the phenomenon of adrenaline sensitization). The pupil, however, did not constrict with intravenous injection of solutions of eserine followed by acetylcholine. Eserine in the conjunctival sac constricted the denervated pupil as much as the normal pupil. Acetylcholine applied locally to either eye caused no response.

The fright reaction was somewhat augmented by resection of the cervical sympathetic trunk or the superior cervical ganglion, a point first noted by Mahoney and Sheehan (1936). The pseudo-Graefe phenomenon and ocular synkinesias appeared after the same interval irrespective of whether the oculomotor and cervical sympathetic nerves were severed simultaneously or seriatim.

Trigeminal nerve.—Simultaneous section of the third and fifth cranial nerves resulted in the usual oculomotor ophthalmoplegia, deviation of the jaw to the ipsilateral side, corneal areflexia, and facial anaesthesia (one animal). The pupil was maximally dilated despite the fact that part of its sympathetic supply via the fifth nerve had been interrupted. Recovery of oculomotor nerve function was not altered in this animal. The ptosis began to decrease on the usual day, the fright reaction was elicited as effectively as in monkeys with only the oculomotor nerve sectioned, and the pseudo-Graefe sign appeared in the 5th post-operative week. Movements of the jaw did not cause any abnormal movements in the eye or its lid.

Trochlear nerve.—In a monkey in which the oculomotor nerve had been sectioned previously and in which some recovery of function had occurred, stimulation of the trochlear nerve caused a distinct nasal and downward rotation of the globe over an arc of 2.0 mm. The rotation of the globe was visible during the movement of the blood-vessels on the bulbar conjunctiva. When the third and fourth cranial nerves were sectioned at one operation, recovery in power of the muscles supplied by the oculomotor nerve was not interfered with. The palpebral fissure began to open after the 6th day and the fright reaction appeared on the 7th post-operative day. The fright reaction, however, differed from that observed in other monkeys, since not only did the drooped eyelid elevate after fright, but the eye-ball moved slightly downward, presumably due to contraction of the denervated trochlearis muscle. The pseudo-Graefe phenomenon appeared at the usual time. Contraction in the levator muscle was always accompanied by a contraction in the internal rectus.

Incomplete section of oculomotor nerve.—The foregoing data indicate that ocular structures following recovery from a complete oculomotor nerve section tend to function *en masse*, individual actions of these muscles being permanently lost. When the oculomotor nerve was only partially cut, for example on its

superior surface, there followed a typical oculomotor ophthalmoplegia, and recovery occurred rapidly and completely save for the pupillary reflexes, which remained sluggish. There was no synkinesias in the lid or eye-ball and no contractions *en masse*. Individual actions of the recovered muscles were present and normal. Further studies of this phase of regeneration could not be carried out on the oculomotor nerve because this nerve or its branches is too inaccessible. For this purpose it was much easier to experiment with the facial nerve.

Facial nerve.—Complete transection of the facial nerve resulted, after time had been allowed for regeneration, in mass movements of all the recovered facial muscles. An incomplete lesion, on the other hand, i.e. a partial or hemisection, resulted in paresis of all the facial muscles, but recovery was rapid and complete. Except in localized areas (and this depended upon which fibres were originally cut) there were no simultaneous massive contractions. Contractions occurred in focal areas and appeared to be true synkinesias. These focal movements occurred whenever the normally innervated muscles supplied by the same but uncut part of the nerve were actively innervated. On the other hand, no synkinesia was noted in these normal muscles when the recovered muscles contracted.

Complete section of the third or seventh cranial nerves resulted in complete paralysis with loss of tone in the ocular and facial muscles. After a period allowed for nerve endings to degenerate, however, these muscles began to regain their tone. Thus 5 or 6 days after the oculomotor nerve was sectioned, a period corresponding with the time necessary for nerve endings to degenerate, ptosis of the upper eyelid began to diminish. The receding ptosis was due primarily to increase in muscle tone of the levator palpebræ. It was not due to activity of Mueller's palpebral muscle, since previous section of the cervical sympathetic trunk did not materially alter the rate of recovery from the ptosis. Similarly the paralysed facial muscles also regained their tone. This recovery in muscle tone could not be due to regenerating nerve fibres, for it appeared even after large blocks of nerve tissue had been resected. More significant, however, was the fact that the increased tone ran closely parallel to progressive increase in sensitivity of denervated muscle to acetylcholine (Bender, 1938).

Sensitivity of denervated muscles to acetylcholine.—The sensitivity of denervated muscles to acetylcholine is well recognized, but few quantitative determinations are available concerning the degree of this sensitivity on the intact animal—certainly no determinations have heretofore been reported in primate forms. Using monkeys with sectioned facial nerves, the denervated muscles were maximally sensitive 4–5 weeks after the nerve section.

Parallel to this increased sensitivity of the denervated muscle to acetylcholine was increased response of these muscles during fright; the fright reaction was also augmented by eserine. After signs of nerve regeneration had manifested themselves (muscle twitches appearing as part of the reflex response), the sensitivity to acetylcholine began to decrease. In other words, as soon as the muscle was influenced by the regenerating nerve, it began to lose its sensitivity to such chemical agents as acetylcholine. The diminution of sensitivity during

functional recovery of the muscle was gradual, extending over a period of several weeks.

Discussion

To account for the mass contractions which follow regeneration of the oculomotor nerve, one must consider the anatomical and functional changes which may accompany regeneration in a single oculomotor neuron unit.

(1) *The cell body*.—Fuchs (1893) thought that the pseudo-Graefe phenomenon was due to spread of impulses in the oculomotor nerve nucleus, i.e. to impulses arriving at non-functioning cells might jump to adjacent active cells. Thus it is conceivable that retrograde degeneration may cause physiological or anatomical changes in the ganglion cell, and that when regeneration of the axon has occurred the metabolism of the cell body may still be upset. Such a theory, however, would not account for the parallel observations on patients with regenerated sensory nerves in which stimulation of one point caused sensation in many points (Ford and Woodhall, 1938). This obviously could not be due to retrograde changes in the centre, or to alterations in the sense organs. Stopford (1926) explained the diffuse and perverse sensations felt after regeneration of sensory nerves on the basis of misdirection of nerve fibres.

(2) *The nerve scar*.—Langley and Anderson (1904), Kilvington (1905), Ramón y Cajal (1928), Howe, Tower, and Duel (1937) proved that during the process of repair the newly formed axis cylinders branch freely and grow indiscriminately into the distal stump, losing their former anatomical arrangements in new plexuses. In such circumstances an impulse intended for one group of muscle fibres may be shunted at the scar to other muscle masses, and the affected neurons when activated may thus cause widespread contraction. Whether all muscles contract to an equal degree depends upon the number of nerve fibres regenerated and how extensively the axis cylinders dichotomize. Examples of such partial contraction in the extra-ocular muscles have been observed in man (Bielschowsky, 1935 ; Ford and Woodhall, 1938). The ptosed eyelid may, for example, move up on attempted downward gaze, or *vice versa*, a phenomenon also explicable on the basis of misdirection. In the monkey it would appear that all muscles supplied by the cut oculomotor generally regain a share of the newly formed axis cylinders. The changes at the nerve scar may fully account for diffusion of impulses ; the normal topography of the nerve trunk may, however, be a contributing factor ; thus Compton (1917), Langley and Hashimoto (1917), and McKinley (1921) have all found internal plexuses within the normal peripheral nerve. Such an arrangement would predispose the regenerating axis cylinders to functional confusion.

These considerations also provide rational explanation of the signs observed in incomplete nerve sections, since a lesion affecting a few fibres in the main trunk would cause local misdirection at the scar.

(3) *The motor end-plate and muscles*.—Degeneration of the nerve endings causes the denervated muscles to become sensitive and contract readily in the

presence of chemical agents such as acetylcholine. After nerve regeneration, however, although the sensitivity of reinnervated muscle to acetylcholine diminishes, there may remain a functional abnormality such as heightened excitability, whereby any impulse reaching the recovered desensitized muscle would result in a contraction. This might account for the well-known persistent contractures observed in patients with Bell's palsy. When tonic impulses reach the facial muscles these altered muscles respond excessively, especially during phasic innervation, when the altered facial muscles contract *en masse*. Denny-Brown and Pennybacker (1938) have studied the post-paralytic facial contracture electromyographically. These records revealed rapid action currents of uniform size and shape. The outbursts which occurred at irregular intervals were of increased frequency following attempted innervation of muscle. Since the bouts of rapid discharge were periodic, they inferred that a focus in the nerve fibre or the motor neuron in the facial nucleus were intensely excited at intervals. Their findings suggested a central origin for the post-paralytic facial contracture.

Signs of acetylcholine sensitization of paretic muscles were, as already indicated, readily demonstrated following nerve section, and the phenomenon no doubt has an important bearing upon the course of functional recovery, especially before functional reinnervation appears. Unless the peripheral ramifications of the autonomic nervous system form a syncytium (Stöhr, 1927), the muscle tone which appears soon after denervation cannot be due to active innervation from other nerves. Resection of all local nerves, avulsion of large blocks of nerve tissue, and repeated section of possibly regenerated nerves do not diminish the resting tone of the affected muscles (Bender and Kennard, 1938).

Not only is there a restoration of a postural tone, but spontaneous electrical activity and fibrillations have been noted in these denervated muscles (Denny-Brown and Pennybacker, 1938). The spontaneous electrical activity was found to be enhanced by eserine (Rosenblueth and Luco, 1938). Tremors or fibrillations in the denervated muscles were also augmented by eserine (personal observations). Evidently, therefore, a chemical agent influencing these muscles must be responsible for the spontaneous activity and contracture. This substance might be related to acetylcholine and found in the body tissues and circulation.

In the foregoing analysis of changes in the motor neuron and muscle, the hypothesis of misdirection of regenerated axis cylinders seems best to explain the abnormal movements in the recovered muscles. The other two factors, that is, disturbances in the cell nucleus and in the denervated muscle fibres, may operate to some extent. It is doubtful whether cortical centres have any direct influence on the abnormal mass movements. General anaesthesia or cortical ablation of the facial or ocular centres do not abolish the movements *en masse*. Long after nerve regeneration is complete, abnormal mass movements persist. Some authors state that the abnormal mass movements can be made to disappear by re-education. In man, as related to the cranial and sensory nerves (Head, 1920), no amount of re-education yields return of

individual function. Sometimes in peripheral motor lesions re-education of a formerly paralysed part occurs, but chiefly through supplementary or trick movements (Pollock and Davis, 1933).

Summary

1. Recovery from intracranial section of the oculomotor nerve in monkeys is characterized by mass movements in all of the muscles supplied by the nerve.

2. The recovery in function of these muscles is not materially affected by section of the fourth or fifth cranial nerves, nor by extirpation of the cervical sympathetic chain.

3. Recovery and the phenomena attendant upon it are most likely due to arborization and misdirection of the regenerated axis cylinders.

4. It is suggested that the early appearance and continual increase in muscle tone which runs closely parallel to the increasing sensitivity of the denervated muscles to acetylcholine is due to a circulating chemical agent similar to acetylcholine in its action.

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