COMMUNICATIONS

THIRD NERVE REGENERATION*†

A CLINICAL EVALUATION

BY

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My first and most pleasant duty is to thank the members of the Irish Ophthalmological Society for inviting me to deliver the Montgomery Lecture for 1957 at this joint meeting with the Society of British Neurological Surgeons. It is an honour that I appreciate deeply and shall always consider as a highlight in my professional life.

The selection of a topic has given me much concern. I am deeply disappointed that I am unable to present something new, but new information is hard to come by. All that I am about to say has been said before; possibly it has not received quite the attention it merits from those of us who, as clinicians, try to utilize basic investigations. My interest in regeneration of the third nerve as an explanation for abnormal eyelid and eyeball movements was stimulated by studies made with Doctor Walter Dandy on saccular aneurysms. This paper deals with acquired third nerve paralysis, and brief mention is made of differential diagnosis.

REGENERATION OF NERVES

Only a few facts regarding nerve regeneration are mentioned here as an introduction to the particular features of third nerve regeneration with which this paper is concerned.

It is established that motor and sensory nerves regenerate; also it seems reasonably certain that autonomic nerves regenerate. Undoubtedly regeneration occurs in peripheral nerves, but it is doubtful that it occurs when interruption has been central.

When a nerve has been severed or crushed, there is degeneration of the axons in the severed fragment. If and when regeneration occurs, there are likely to be more axons in the regenerated nerve than were present before the nerve was interrupted. Axons develop from the cut end of the nerve which has been severed and from collateral nerves which have not been severely damaged (Nageotte, 1932). There is free sprouting of new fibres from the central stump, and cords of Schwann cells form in the peripheral

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segment of the nerve, so that the new fibres are conducted to the end organ (Young, 1942). The newly-formed neurons reach the empty tubes (Schwann's tubes) which before the degeneration contained functioning neurons (Gutmann and Young, 1944; Edds, 1953). In the distal end of the severed nerve there is a tendency toward endoneurial tube shrinkage (Sunderland and Bradley, 1950). Regenerating axons have the capacity to bridge long gaps in damaged nerves as has been shown by Sunderland (1953), who supported the idea that the distal stump influences the growth and position of the regenerating axons. There is some evidence that chemical agents released by the denervated muscle, at least in the instance of motor nerves, may play a part in the regeneration phenomenon (Edds, 1953).

Ford and Woodhall (1938) studied regeneration in cranial, spinal, and autonomic nerves. Their findings as regards the facial and oculomotor nerves are described subsequently in this paper. They described the "crocodile tear" and auriculotemporal syndromes as dependent upon the misdirection of regenerated fibres. Regeneration of the medial and ulnar nerves resulted in misdirection and mass action as well as sensory changes which are not considered here. An odd example of misdirection was described by Robinson (1951), who found, in individuals who had suffered a brachial plexus injury at birth, that there were movements in the paralysed limb associated with deep inspiration. These movements varied according to the nature of the brachial plexus palsy.

As regards the newly-formed axons in the regenerated nerve, Ford and Woodhall (1938) cited an experiment of Ramon y Cajal (1928). He severed the sciatic nerve of a cat where it was composed of two separate nerve trunks, the peroneal and the tibial. The regenerating fibres of the tibial nerve entered the distal stump of both the tibial and the peroneal nerve, and those arising in the proximal stump of the peroneal nerve entered both distal stumps in the same way.

Cajal stated:

"Those sprouts which reach the peripheral stump enter it in great disorder; some sheaths have no sprouts and the great majority, if not all, of the sheaths, instead of receiving the outgrowth of the same axon which was present in them before the operation, are invaded by sprouts which have come from axons in other regions of the central stump. Thus, the observed facts compel us to reject the supposition of those authors who believe that the newly-formed fibre infallibly ends in the old sheath of the peripheral stump and unerringly restores the old terminal arborization, thus preserving the anatomical and physiological individuality of the pre-existing conductor. On the contrary the errors and incongruences are so many that one wonders whether the whole mass of sprouts which penetrate into the peripheral stump is not entirely superfluous, seeing that the connections between central neurons and the peripheral structures which formed, since the embryonic period, such as intimate anatomical and dynamic whole, are now so disturbed and confused. Moreover, in cases of rapid nervous reunion after hemisection or complete sections with small scar, sensibility and movement are only more or less imperfectly restored." (Ford and Woodhall, 1938.)

AETIOLOGY AND OCCURRENCE OF THIRD NERVE PARALYSIS

Acquired paralysis of the third nerve, according to my experience, originates in the following order of frequency:

(1) aneurysms;	(4) diabetes;
(2) trauma;	(5) inflammation;
(3) tumour;	(6) ophthalmoplegic migraine.

(1) Aneurysms have accounted for more examples of regeneration of the third nerve in my practice than has any other aetiological factor. From the statistical point of view this is of no importance because it would vary widely in different centres.

(2) Trauma is a frequent cause of third nerve paralysis. Practitioners who are engaged in an industrial practice often see such cases. Turner found third and sixth nerve paralysis to occur about equally often as a result of war trauma.

(3) Tumour is a frequent cause of third nerve paralysis. Usually in such cases the paralytic involvement is not an isolated one. In my experience regeneration of the third nerve with misdirection of fibres is rarely present as a result of tumour.

(4) and (5) Diabetes and inflammation are infrequent causes of third nerve paralysis. I have seen these aetiologies about equally often. I have not had experience with total third nerve paralysis with herpes zoster; seemingly, incomplete involvement is the rule.

(6) Ophthalmoplegic migraine is quite a rare affection. In the few cases I have encountered third nerve paralysis has been present.

PROGRESS OF THIRD NERVE PARALYSIS.—Any of several developments may characterize third nerve paralysis:

(1) There may be complete recovery. Presumably either no or only slight degeneration has occurred.

(2) The paralysis may persist unchanged.

(3) Only a change in the pupil may remain as evidence of the paralysis.

(4) There may be incomplete recovery as regards the ophthalmoplegia.

(5) There may be recovery with evidence of misdirection of the regenerated fibres, and in such cases there may be pupillary changes which are characteristic.

The situation as regards the pupil in cases of third nerve paralysis is briefly stated:

(a) There may be a return of the pupil to normal;

(b) The pupil may remain widely dilated and fixed to light stimulation, both direct and consensual;

(c) It may become smaller than its normal fellow of the opposite side, and it may remain sluggish to light stimulation;

(d) The pupil may become of Argyll Robertson type when it shows evidence of misdirection of regenerated fibres (Ford, Walsh, and King, 1941).

PHENOMENON OF MISDIRECTION OF REGENERATING FIBRES.—I have used this title as being possibly more informative than “aberrant regeneration”, but in fact the terms are synonymous. Although we are here concerned with the phenomenon as it is observed after third nerve paralysis, brief mention is now made of regeneration of the seventh nerve because such

regeneration received much study long before the phenomenon as it affects the third nerve received any considerable attention. It would be expected that the pattern of regeneration of these two nerves might be similar, because both nerves supply several muscles. It might be anticipated that regeneration of the seventh nerve could be responsible for changes in glandular function, and this is seen in the instance of "crocodile tears". Since the third nerve innervates the pupil, it would seem likely that pupillary anomalies could develop on the basis of regeneration, as does in fact occur.

In the case of the seventh nerve partial recovery from paralysis occurs in many instances within several months after the nerve has been paralysed. Such recovery is characterized by the development of associated movements which occur in varying degree, yet have a fairly constant pattern. When an effort is made to approximate the eyelids on the affected side, there is an associated contraction of muscles at the corner of the mouth and of the homolateral side of the chin. When an individual with facial paralysis whose facial nerve has regenerated attempts to bare the teeth, the eyelids close on the homolateral side (Fig. 1).

FIG. 1.—Regeneration of right facial nerve.

(A) Increased tone in the right facial muscles.

(B) An attempt to bare the teeth results in closing the right eye.

Lipschitz (1906) suggested that these associated movements, which are involuntary, were due to the misdirection of regenerating fibres. He acknowledged that the concept had already been mentioned by Lamy (1905). Ramon y Cajal (1928) supported the idea, and for a time it was accepted by Wartenberg (1946), but he later rejected the idea of misdirected (or aberrant) fibres in the regeneration of both the seventh and the third nerves. It may also be remarked that, when seventh nerve paralysis develops later after injury or when it clears early (that is, within a matter of 2 or 3 weeks), there usually is no remaining evidence of paralysis.

REGENERATION OF THIRD NERVE.—The third nerve normally supplies the levator muscle of the upper eyelid, the medial, superior, and inferior rectus muscles, and the inferior oblique muscle. In addition, it supplies the sphincter of the pupil. The superior branch of the nerve supplies the levator and the superior rectus muscles; the inferior branch supplies all other muscles supplied by the third nerve, including the pupil. The fibres which proceed to the pupil are ultimately carried in the branch to the inferior oblique muscle. The upper eyelid is elevated through the contraction of the levator muscle. When elevation of the lid occurs, there is a synchronous relaxation of the orbicularis muscle (innervated by the seventh nerve). The upper eyelid is lowered when the eye is closed by contraction of fibres of the orbicularis, and there is synchronous relaxation of the levator. The mechanism of this downward movement of the upper eyelid (following movement) when the eye is lowered is not fully understood, but it is of interest that it occurs in the presence of a facial nerve paralysis. In part, the following movement is due to gravity. In part it is due to relaxation of the levator. The close association (osmotic attraction) between the eyelid and the eyeball may explain part of the following movement. The eye is adducted principally by the medial rectus muscle but in addition the superior and inferior rectus muscles have slight adducting power. When the medial rectus muscle is contracted, there is relaxation of the lateral rectus muscle. Conversely, when the lateral rectus is utilized there is relaxation of the medial rectus. All this is in conformity with the theory of reciprocal innervation of the ocular muscles (Sherrington, 1894): if one ocular muscle is contracted its opponent is relaxed.

During regeneration of a damaged third nerve, axons which were originally destined for the levator may in some instances reach that muscle, but other such axons may reach the medial or inferior rectus or the inferior oblique muscles, axons destined for the superior rectus may reach the inferior rectus, and so on. Thus it would seem that with the third nerve, as with the seventh, a mass contraction might develop, and this does in fact happen.

In a classical case of regeneration of the third nerve characterized by misdirection of regenerated fibres, the upper eyelid is elevated when the eyeball is adducted, voluntarily or involuntarily. It is this elevation of the upper eyelid which is so frequently described as the pseudo-Graefe phenomenon. When an effort is made to look up or down with the affected eye, the attempted movement is not obtained because contraction of the superior rectus, occurring at the same time as contraction of the inferior rectus (as well as of other muscles innervated by the third nerve) or *vice versa*, makes vertical movement of the eye impossible. In these circumstances the eye turns in, and the upper eyelid becomes elevated or remains so (Fig. 2, overleaf).

On the basis of reciprocal innervation, as enunciated by Sherrington and as illustrated above, when the affected eye is *abducted* the upper eyelid would be lowered and the outward movement of the eye would be of full range.

FIG. 2.—Left third nerve palsy. With the eyes in the primary position they appear normal. When an effort is made to adduct the right eye or to direct the gaze downward, the left upper eyelid is raised and the left eye fails to move down (Gowers, 1879).

Associated with the abnormalities of ocular movement just described, a type of Argyll Robertson pupil may develop as part of the misdirection syndrome. The ultimate features of the pupil after third nerve paralysis have already been stated. With the phenomenon now under consideration, the pupil, which may be large or small, fails to react to direct light. It becomes narrowed when the eye is adducted, whether fixation is on a near object (convergence) or on a distant object. Presumably the iris sphincter receives not only pupillary fibres but also others originally destined for the medial rectus or other muscles supplied by the third nerve.

When a “mass movement” occurs in fully-developed cases with misdirection a low-grade enophthalmos is developed. This is explained on the basis of the retracting influences of the contracted recti muscles. This feature has not been described previously so far as I am aware. I hesitate somewhat to mention it since I have been unable to measure the enophthalmos satisfactorily in any case, but Dr. Frank R. Ford is convinced, with me, that it is part of the fully-developed syndrome.

The misdirection phenomenon does not always occur in classical form as has been described above, since presumably, to obtain “full” misdirection,

the third nerve paralysis would have to be complete; but fragmentary examples of the phenomenon are often observed.

SOME EARLY STUDIES OF THIRD NERVE REGENERATION.—The earliest contributions were made in the 1890s. It was at this time that the unfortunate eponym, “pseudo-Graefe sign”, was given to the phenomenon of upper-lid retraction. As Wartenberg (1946) noted, after nerve regeneration the upper eyelid does not only “lag” (wherein the title would be reasonable) when an effort is made to lower the eyeball on the affected side, but (particularly when adduction is also attempted) it becomes sharply elevated. Such a movement is obviously an associated movement; it is involuntary and cannot be suppressed. Gowers (1879), in describing several ocular movements, pictured partial recovery from third nerve paralysis as characterized by retraction of the upper eyelid (Fig. 2). Fuchs (1893, 1917) also described the phenomenon, accepting the hypothesis of aberrant regeneration as has been outlined above. He thought that there was retrograde degeneration and that the phenomenon was associated with nuclear involvement. The abnormal behaviour of the upper lid has since often been referred to as Fuchs’s sign. Wilbrand and Saenger (1900) showed retraction of the upper eyelid in an individual who exhibited a total third nerve paralysis; the abnormal behaviour of the upper eyelid was attributed to the action of the frontalis. Bielschowsky (1935) remarked upon retraction of the upper eyelid as occurring in some cases of third nerve paralysis, and stated that this was an evidence of regeneration and entirely different from what he had described as cyclic oculomotor paralysis in which there is recurrent elevation of the upper eyelid on the affected side. He suggested that most cases of misdirection originated as the result of injury at the base. He pointed to the similarity between the retraction of the lid in these cases and the paradoxical elevation of the upper eyelid which occurs in congenital cases of jaw-winking (Marcus Gunn phenomenon). He described five cases (three of fracture, one of syphilis, and one with aetiology not determined) and produced four series of photographs. In all instances pronounced elevation of the upper eyelid occurred when the affected eye was adducted, and the elevation was greatest when, at the same time, an effort was made to look down.

Bender and Alpert (1937) and Bender and Fulton (1939) have made valuable contributions. Bender (1954) subscribed to the idea of faulty regeneration of the third nerve; in this communication he suggested the dual innervation of the orbicularis (third and seventh nerves). Bender and Fulton (1939) described experimental section of the third nerve in monkeys. Regeneration was characterized by ophthalmoplegia and lid retraction as has already been outlined. Inability to look up or down resulted from simultaneous contraction of the superior and inferior rectus muscles. By sectioning the superior rectus muscle, an experimental animal could move

the eye downward; by sectioning the inferior rectus, the eye could be moved upward. They also observed the Argyll Robertson pupil in their experimental animals.

I have mentioned regeneration of the third and seventh nerves according to the hypothesis of Lipschitz (1906) as affecting only peripheral nerves. What may be considered as an alternative concept was described by Wartenberg (1946), who criticized the idea of peripheral misdirection of regenerating fibres and attempted to show that the associated movements described above represent the influence of a central lesion which has resulted from a retrograde degeneration. Years earlier Fuchs (1917) had suggested that a central lesion was responsible, and that it served to spread impulses from the cerebrum to various part of the third nerve nucleus.

A third possible mechanism accounting for the characteristic associated movements was mentioned by Bender (1954) in commenting upon a bilateral case of aberrant regeneration of the third nerve, which was presented and described by Norton and Wetzig (1954). The hypothesis is that the denervated muscle has become sensitized to some agent, chemical, mechanical, or electrical.

Levin (1952) made a contribution of prime importance; he produced histopathological evidence that seems to establish the concept of peripheral misdirection. He remarked that anatomical studies on the third nerve after regeneration had been made only by Köppen (1894), who had studied a case characterized by lid retraction and found changes in the peri-aqueductal grey matter, but no changes in the nerve cells, tracts, or nerve roots. Levin's patient, an elderly woman, was shown at autopsy to have had an aneurysm arising from the left internal carotid artery at its junction with the posterior communicating artery. This aneurysm had caused haemorrhages on several occasions, and death ultimately occurred. Anomalous eye movements had been observed on the side of the aneurysm with elevation of the upper eyelid when adduction was attempted. Adduction was not fully performed. Upward and downward movements of the eye were somewhat diminished in amplitude. There was mild ptosis on abduction of the eye. There were no pupillary changes suggesting an Argyll Robertson pupil. Levin remarked upon the third nerve paralysis never having been complete, and that lid retraction in such a case was remarkable. He felt that probably only a few third nerve fibres were affected at any time so that there was never great loss of function. At the autopsy neuromatous changes were found in the roots of the oculomotor nerve (Figs 3 and 4, opposite). Cells were collected in interlacing fascicles with palisaded nuclei; each cell was surrounded by an endoneural sheath. In cross-section views axis cylinders were seen penetrating the tissue.

ELECTROMYOGRAPHY AND NERVE REGENERATION.—Recently electromyography has been used in the study of the extra-ocular muscles. The potentials

FIG. 3 (From Levin, 1952).

(A) Spiral formation of neurites and cells arranged about a minute hollow tube. Above is a portion of retiform tissue (fasciculated tissue in cross-section) composed of tubes, fibres, and nuclei. Bodian preparation, counterstained with Masson's trichrome stain.

(B) Elongated cells (tubes) incorporating nerve fibres. Note varicosities on fibres. Bodian; $\times 1,000$.

FIG. 4 (From Levin, 1952).—Regenerating fascicle in oculomotor nerve root with elongated cells and fibres arranged in interlacing bundles.

(A) Appearance with routine cell stain, showing palisading of nuclei; haematoxylin and eosin; $\times 165$.

(B) Nerve-fibre preparation, showing prominent fibre component. At top of figure is a bundle of irregular, but otherwise intact, nerve fibres. Bodian; $\times 165$.

(C) Reticulum preparation. Reticulin fibres are fewer and more delicate than axons. At the top the endoneurium is densely impregnated. Perdrau's modification of Bielschowsky's method; $\times 165$.

of muscles are recorded electronically after tiny electrodes have been inserted directly into the muscle being examined. Electromyography provides proof of degeneration in some instances when there are no clinical evidences of it. When the nerve-muscle unit is undergoing pathologic change one can detect abnormal potentials, erratic firing, bursts of discharge, or rapid fatiguing. Examination of muscle activity by this technique supports the concept of misdirection of regenerated third nerve fibres. Björk (1954a, b) is the pioneer in this field, and in the United States Breinin is a leading authority.

Recently we have attempted such studies in an individual who probably harboured an aneurysm and had had a haemorrhage on one occasion. She exhibited clinical evidence of the misdirection phenomenon after third nerve paralysis and regeneration. This patient at rest had a complete ptosis, and some limitation of upward, downward, and medial gaze in the affected eye. The pupil was semidilated and fixed to light, but when an effort was made to direct the eye medially and downward, the upper eyelid retracted and the pupil narrowed (Fig. 5 A, B, C).

FIG. 5 (A).—Record from levator muscle with eyes directed straight forward. Action potentials are low but definitely present and appear quite regular. When an effort is made to look up, the action potentials become irregular and appear to discharge in bursts, indicating abnormal activity.

FIG. 5 (B).—Record from levator muscle. The patient is looking down. The activity in the levator is recognized.

FIG. 5 (C).—Records from levator and frontalis muscles simultaneously. The patient was asked to look up. By far the greatest activity is seen in the frontalis, but there is increased, though rather irregular, activity in the levator.

Dr. G. M. Breinin has given me a great deal of help with the electromyography, and I am indebted to him for the case summaries and tracings which are reproduced below (Breinin and Moldaver, 1955).

Case Reports

Case 1, Diabetic Neuropathy.—A 72-year-old diabetic woman developed a total left third nerve palsy with orbital pain. The eye sat at the outer canthus but could be adducted almost to the midline. Peripheral polyneuritis was present. Very faint activity in the medial rectus was generated on adduction and no activity was present on abduction. A tiny remote unit was detected in the levator. No fibrillation was observed. The condition improved over a period of months (Fig. 6).

FIG. 6 (From Breinin).—Electromyogram of medial rectus (Case 1). Very tiny activity present.

Case 2, Probable Diabetic Neuropathy.—A 60-year-old man developed orbital pain on the right side. One week later an external third nerve paralysis developed with some retention of elevation and depression. This improved in 6 weeks. A glucose tolerance test was borderline. Electromyography of the right medial rectus showed slight activity in adduction with a tiny single unit firing. No activity was present in abduction. No fibrillation was observed (Fig. 7).

FIG. 7 (From Breinin).—Electromyogram of right medial rectus (Case 2).

- (A) Abduction—no activity.
- (B) Slight adduction—very faint activity.
- (C) Maximal effort at adduction—tiny potentials.
- (D) Adduction—runs of tiny single units.

Case 3, Diabetic Neuropathy.—A 60-year-old diabetic female developed a bilateral ptosis without other extra-ocular muscle involvement. Electromyography of the levator revealed no activity. The Tensilon (Edrophonium) test was completely negative (Fig. 8, opposite).

Case 4, Traumatic Third Nerve Palsy.—A 67-year-old man had had a traumatic left third nerve palsy 3 weeks before the examination. There was no electromyographic activity in looking left but much single unit and polyphasic unit activity in attempted adduction. Many of the units were of large amplitude (Fig. 9, opposite).

Case 5, Aberrant Third Nerve Regeneration.—A 30-year-old man suffered a traumatic third nerve palsy with a fractured skull; 4 months later adduction was good and elevation of 10°–12° was present but depression was very slight. The pupil constricted on adduction and widened on abduction. No lid retraction occurred. Adduction occurred on gaze up and down. Electromyography revealed simultaneous activity of the medial rectus, inferior rectus and inferior oblique on gaze up and down. The oblique recruited

FIG. 8 (From Breinin).—Electromyogram of right levator (Case 3).

(A) Before Edrophonium } no activity.
(B) After Edrophonium }

FIG. 9 (From Breinin).—Electromyogram of medial rectus, adduction in different electrode positions (Case 4).

(A) Tiny activity.
(B) Large polyphasic unit.
(C) Small polyphasic unit.

on adduction and was inhibited on abduction. The medial rectus also exhibited large activity in abduction (anomalous innervation). The aberrant process appeared to involve primarily the lower division of the oculomotor nerve (Fig. 10, *a, b, c*, overleaf).

FIG. 10(a).—Case 5 (Breinin). Electromyogram of left inferior oblique (above), and integrator (below).

Fixing left up and in } equal activity.
Fixing right down and in }

[The tracing shows proper activity on fixing left up and in. The activity on fixing right down and in should not be present unless there is misdirection.—F. B. W.]

FIG. 10(b).—Case 5 (Breinin). Electromyogram of left inferior oblique (above), and left inferior rectus (below).

Fixing left down } both active out of field.
Fixing right up }

[Upper left and lower right show abnormal activity and suggest misdirection.]

FIG. 10(c).—Case 5 (Breinin). Electromyogram of left inferior oblique (above), and left medial rectus (below).

(A) Primary position } both increase.
(B) Adduction }

(C) Abduction—oblique inhibited while medial rectus increases anomalously.

Case 6, Traumatic Third Nerve Palsy.—A 17-year-old boy suffered a traumatic external third nerve palsy; 2 months later practically no vertical movement was possible but a good range of horizontal movement was present with fusion. Simultaneous activity was present in the medial rectus and inferior oblique. Very little activity was present in the inferior rectus (Fig. 11).

FIG. 11.—Case 6 (Breinin). Electromyogram of left medial rectus (above), and left inferior oblique (below). Both recruit from primary position to gaze up.

Case 7, Traumatic Third Nerve Paralysis.—The patient suffered a fractured skull in October, 1956. There was total paralysis of the right third nerve; 7 months later lateral movements of the eye were full but the eye could not be moved up or down. The right lid showed partial ptosis. It elevated sharply when the eye was adducted and to a lesser degree when an effort was made to look down. The pupil was fixed in mid-dilation (Fig. 12a, b).

FIG. 12(a).—Case 7 (Breinin). Electromyogram of levator in aberrant third nerve regeneration. Left—primary position. Right—adduction.

FIG. 12(b).—Case 7 (Breinin). Electromyogram of right inferior oblique in aberrant third nerve regeneration.

(A) Left—primary position.	Right—adduction.
(B) Left—abduction.	Right—elevation (attempted).
(C) Depression (attempted).	

FIG. 12(c).—Case 7 (Breinin). Electromyogram of right medial rectus in aberrant third nerve regeneration.

(A) Left—primary position. Right—adduction.
(B) Left—elevation. Right—depression (attempted).

FURTHER CLINICAL STUDIES ON THE MISDIRECTION OF REGENERATED THIRD NERVE FIBRES.—In my private files I found the following records concerning third nerve regeneration:

- 17 patients with intracranial aneurysms;
- 14 cases of trauma;
- 4 cases of inflammation;
- 4 diabetics;
- 3 individuals who suffered from ophthalmoplegic migraine;
- 3 cases of intracranial tumour;
- 3 cases of undetermined aetiology.

In a great many instances patients with third nerve paralysis or paresis were seen only once or during a short period and in consequence they offered nothing as regards regeneration.

Cases of acquired third nerve paralysis may be divided into two groups:

- (1) Those with no evidence of the misdirection of regenerated fibres;
- (2) Those in which such evidence is apparent.

(1) Acquired Third Nerve Paralysis without Misdirection

(a) *Diabetes*.—My series of four cases showed what is now generally well known: individuals with diabetes of long-standing may develop third nerve paralysis (Waite and Beetham, 1935; Weinstein and Dolger, 1948). In many instances diabetics who exhibit third nerve paralysis have complained of severe pain at the onset; furthermore, the pain is likely to have had the precise distribution of that which regularly characterizes anteriorly situated aneurysms. In consequence, when an individual with diabetes develops a third nerve paralysis aneurysm is suspected. Cogan (1956) suggested that

some vascular process explains the pain. Often the diabetes is of long-standing and in many cases a retinopathy is present.

I have observed one patient in whom there was a third nerve paralysis first of one, and then of the other eye. This case was reported by Eareckson and Miller (1952). Aneurysm was suspected but arteriography showed nothing remarkable. Within a matter of several weeks there was a complete recovery without evidence of misdirection of regenerated fibres. Then third nerve paralysis with sparing of the pupil made its appearance on the opposite side and again the pain was precisely that which occurs with aneurysm. Within a few weeks there was complete recovery from the third nerve paralysis. The case is particularly noteworthy in that, although all the extra-ocular muscles were paralysed, there was total absence of internal ophthalmoplegia in each eye.

An explanation for third nerve paralysis in diabetes has been conjectural since its first description in 1866 (Dreyfus, Hakim, and Adams, 1957). Peripheral neuritis comes to mind, but it seems unlikely that such an involvement would be unilateral as usually occurs.

An opportunity to do a *post-mortem* study enabled Dreyfus, Hakim, and Adams to present us with histopathological evidence.

Their patient was a 62-year-old woman who was known to have had diabetes for 10 years. Probably the diabetes was poorly regulated. Five weeks before admission to hospital she developed left ptosis with left-sided headaches which persisted. The left eye could not be adducted beyond the midline and vertical movements were very slight. Ptosis was complete, but the pupil was spared. In order to rule out an aneurysm a left carotid arteriogram was made. After a short time the patient died.

Dreyfus, Hakim, and Adams found a fusiform enlargement of the left third nerve in the retro-orbital (intracavernous) portion of the third nerve with the enlargement affecting approximately one centimetre of nerve. Principally centrally there was destruction of some of the axons and myelin sheaths. There was an increase in the connective tissue of the nerve and a suggestion of regeneration in the area of destruction. There was Wallerian degeneration in the distal segment of nerve and minimal evidence of axonal reaction in the left third nerve nucleus.

This autopsied case characterized by pupillary sparing is of interest in regard to the description of the pupillomotor fibres occupying a superior and peripheral position in the nerve between the cavernous sinus and the midbrain (Sunderland, 1952). Sparing of the pupil in diabetic third nerve paralysis has additional interest when it is recalled that in diabetics there is occasionally encountered a pupil which is rigid to light and in some instances cannot be differentiated from an Argyll Robertson pupil. With third nerve paralysis associated with aneurysm, trauma, or tumour, the pupil is almost invariably involved. I recall having had a case of aneurysm and a case of tumour in which third nerve paralysis was complete except in that the pupil was completely spared.

Dreyfus, Hakim, and Adams (1957) injected Neoprene (a polymer of chloroprene) into the basilar and carotid arteries of cadavers in order to study the blood supply of the third nerve. They found small arteries arising from the posterior cerebral or superior cerebellar arteries entering the nerve where it passes between these arteries. At the orbital end of the nerve they

demonstrated the blood supply to the nerve from the ophthalmic artery. They were unable to demonstrate the blood supply to the intracavernous portion of the third nerve. They suggested incomplete ischaemia as a possible cause of diabetic third nerve paralysis.

It seems significant that the misdirection phenomenon occurs so rarely with diabetes where there is third nerve paralysis. In these cases recovery from paralysis begins earlier than when the paralysis is due to aneurysm or trauma. Cogan (1956) stated that, if there is recovery from oculomotor paralysis within 6 weeks, aberrant regeneration does not occur. In the autopsy report by Dreyfus and others (1957), the completeness of the paralysis with the incomplete involvement of the nerve was commented upon. Dreyfus, in a personal communication, stated that he had not seen any report of aberrant regeneration in diabetics with third nerve palsy. Also, he remarked that he saw no reason why such regeneration should not develop after a lesion. The almost total absence of response to electromyography in these cases during the earlier stage is of interest (Figs 5, 6, and 7).

(b) *Ophthalmoplegic Migraine*.—This affection, which may be characterized by third nerve paralysis, is seen infrequently. In each of my three patients who seemed to qualify for this diagnosis, there were several attacks of third nerve paralysis. In one, a child aged 12, there was a history of recurrent headaches associated with third nerve paralysis commencing at 3 years of age. When we observed him he had had his sixth attack and the third nerve paralysis on the right seemed complete. In these cases total third nerve paralysis including pupillary involvement seems to be the rule. Recovery from the paralysis commences within a few weeks at the most and is always complete so far as I am aware. There has been no evidence of misdirection of fibres in my cases or in any others that I know about.

Harrington and Flocks (1953) recently suggested that herniation of the temporal lobe is a mechanism which may explain ophthalmoplegic migraine. While this idea may have merit certainly the mechanism has not been established. It is of interest that the herniation of the temporal lobe occurs very often with chronic subdural haematoma and certainly in this circumstance total third nerve paralysis is exceedingly uncommon.

In the cases which I have included under ophthalmoplegic migraine, aneurysm seems to have been eliminated in all instances, and in this regard the absence of misdirection of regenerated fibres has importance.

(c) *Temporal Arteritis*.—I had no patients in this category, but Murray (personal communication) has observed third nerve paralysis in a 66-year-old woman who was shown by biopsy to suffer from temporal arteritis. On the side of the involvement she developed a total third nerve paralysis excepting that the pupil was spared. Within 6 weeks recovery from the paralysis was almost complete and there was no evidence of misdirection.

(2) Acquired Third Nerve Paralysis with Misdirection

(a) *Intracranial Aneurysm*.—Aneurysms situated at the base anteriorly are characterized by a symptomatology which is generally well known. Often there is pain in the temporofrontal region with or without loss of consciousness, and frequently blood is found in the spinal fluid. If, in addition, there is a third nerve paralysis, the diagnosis of aneurysm is almost a certainty. The onset of third nerve involvement varies widely. In many instances, evidence of the onset of oculomotor paralysis occurs within a matter of hours after the onset of pain but in some instances the nerve palsy may appear days, or even weeks, after the initial signs. In both circumstances the third nerve paralysis in these cases is likely to become complete with a dilated and fixed pupil. It seems obvious that the third nerve paralysis may result from pressure, from interference with blood supply to the nerve, or from intra-neural haemorrhage. Which of these factors is responsible usually is not established. As regards regeneration of the paralysed nerve, it can be said with assurance that it usually develops and that evidence of misdirection of fibres is almost invariably present. However, I have seen in an individual with a proven aneurysm a third nerve paralysis which remained total and unchanged 10 years after the diagnosis was established.

The misdirection phenomenon may be fully or only partially developed. In some instances the picture varies widely from that which has been described herein as classical. Instead of regenerated fibres being fairly generally distributed to the muscles, an uneven distribution may account for bizarre ocular movements. Cogan (1956) remarked upon such an unusual circumstance. He stated that, if the levator muscle receives fibres originally connected with the superior rectus muscle, the eyelid rises with normal voluntary upward movements of the eyes and also with involuntary upward movements (Bell's phenomenon) on attempted closure of the lids, and at other times the affected eyelid shows ptosis. "In other words, the lid opens widely when an attempt is made to close it" (Fig. 13).

FIG. 13.—There has been left-sided third nerve paralysis (Gifford, 1939; see Cogan, 1956).

(A) Left upper lid partially elevated by contraction of frontalis.

(B) Ptosis on left is nearly complete.

(C) Paradoxical elevation of left upper lid during closure of right eye.

A remarkable situation is shown in Fig. 14 (Bielschowsky, 1935). In this patient, efforts to look up resulted in the affected eye turning sharply downward. Probably, in the affected eye regenerated fibres had failed to reach the superior rectus muscle and were concentrated in the inferior rectus. Bielschowsky's explanation in this particular case was that the downward movement was produced through the action of the fourth nerve; this seems unlikely and the regeneration syndrome is probably the proper answer.

FIG. 14 (Bielschowsky, 1939).

- (A) Left oculomotor paralysis with left upper lid completely relaxed.
- (B) Maximum contracture of left superior oblique prevents left eye from reacting to elevation impulse, the left upper lid being raised considerably.
- (C) Maximum innervation of depressor muscle causes slight lifting of upper lid.
- (D) Laevoversion impulse, with complete relaxation of left upper lid.
- (E) Dextroverson impulse, with maximum retraction of left upper lid.

Incomplete syndromes occur not infrequently. Elevation of the upper eyelid (the so-called pseudo-Graefe sign) is certainly the most early recognized manifestation of the syndrome. In the case reported by Levin (1952), it was the most prominent evidence of the regeneration process (Figs 3 and 4). Not uncommonly there is some limitation of adduction. Vertical movements may be present in some degree, and I think that upward movement is

more likely to be abolished with incomplete syndromes than downward movement.

Probably sufficient has already been said regarding the pupil. I have no case record in which an Argyll Robertson type of pupil has been the sole remaining evidence of the misdirection of regenerated fibres in a case of third nerve paralysis. In all likelihood such cases exist.

(b) *Trauma*.—There is nothing about the syndrome of regeneration in these cases that differs from that observed in association with aneurysm, excepting that with trauma the paralysis occurs immediately. After trauma the syndrome may be classical and complete, including changes in the pupil, or it may be incomplete. In my fourteen cases there were included two attributed to birth trauma, and in one of these the syndrome was complete.

Traumatic third nerve paralysis not infrequently becomes a medico-legal problem. I have had experience with three such cases, in all of which the syndrome was complete. In each one it was accepted that from the practical standpoint the injured eye was lost (visual acuity in all three was excellent) because of the diplopia present in all fields.

(c) *Intracranial Tumour*.—It has been difficult for me to understand how rarely misdirection of regenerated third nerve fibres occurs in association with cerebral tumours. A child aged 7 exhibited third nerve palsy as an early evidence of pituitary tumour, and after operation a classical misdirection syndrome developed.

(d) *Inflammation*.—In three of four patients who exhibited the syndrome as a result of inflammation, there was a history of treated syphilis. The fourth, a child aged 2, obviously suffered from septic cavernous sinus thrombosis. The blood culture was positive. The child was the first youngster in the Harriet Lane Home to receive sulpha drugs. He made a remarkable recovery, but developed a classical misdirection syndrome.

(e) *Undetermined Aetiology*.—My three cases in this category were not remarkable. In none was there pupillary change.

It is opportune to remark here that we have observed a 14-year-old Negro boy who was admitted to hospital because of unilateral ptosis, said to have been present since birth. He exhibited a unilateral jaw-winking (Marcus Gunn) phenomenon. There was a double elevator palsy on the side of the ptosis. When the eye was adducted, the upper lid was sharply elevated. The elevation of the upper lid could have been explained on the basis of misdirection of regenerated fibres. It seems possible that both syndromes were present in this patient.

PROGNOSIS AND TREATMENT

When regeneration has developed, there is no possibility of the signs of misdirection disappearing spontaneously.

In the fully developed syndrome, surgical therapy cannot possibly provide

single vision and free motility of the affected eye. In occasional instances, as for example when a ptosis has persisted, a surgical procedure may be employed to advantage.

SUMMARY

Regeneration of the third nerve in some instances is associated with abnormal ocular and lid movements. In the fully developed misdirection syndrome, a fairly constant pattern of abnormality is seen. Our present knowledge concerning the misdirection syndrome is outlined: usually there is evidence of misdirection when the third nerve paralysis has been associated with aneurysm or trauma; it is less frequent when it is the nerve that has been affected by intracranial tumour or inflammation; it does not occur when third nerve paralysis results from ophthalmoplegic migraine or diabetes. Once the regenerating nerve fibres have taken the wrong course there is no likelihood of the condition regressing spontaneously. Surgical treatment may be of value in cases of persistent ptosis.

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