

## Historical Review

# James Sharpe's Contributions to Neurology and Neuro-ophthalmology: A Posthumous Tribute 10 Years On

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**ABSTRACT:** Dr. Sharpe was a leading eye movement researcher who had also been the editor of this journal. We wish to mark the 10th anniversary of his death by providing a sense of what he had achieved through some examples of his research.

**RÉSUMÉ :** Contribution du D<sup>r</sup> Sharpe à la neurologie et à la neuro-ophtalmologie : hommage posthume dix ans plus tard. Le D<sup>r</sup> James Sharpe, chef de file en matière de recherche sur le mouvement des yeux, était également rédacteur en chef de la revue. Aussi désirons-nous, à l'occasion du 10<sup>e</sup> anniversaire de sa mort, présenter quelques-uns de ses travaux de recherche qui donneront une idée de l'ampleur de ses réalisations.

**Keywords:** Dr. James Sharpe; Neurology; Neuro-ophthalmology; Tribute

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Jim Sharpe died 10 years ago (1941–2013). He was a larger than life figure in medicine. Even more than his critical and groundbreaking research of eye movements, his editorship of this journal and chairmanship of the University of Toronto's Division of Neurology, his greatest achievement was spawning generations of fellows who went on to become department chairs and leaders in their respective fields. His publications included collaborations with his fellows; the neuro-ophthalmic luminaries Glaser, Hoyt, Daroff, Kline, Trobe; and numerous other medical subspecialists and scientists. One of us (FT) invited several former Sharpe fellows to try to convey a sense of Jim's prodigious contributions by means of selected works.

Those works established the following: (a) the pathway for smooth pursuit, (b) the neuroanatomy of monocular temporal hemianopia, (c) that fixation, smooth pursuit, and VOR cancellation are separate ocular motor systems, (d) the patterns of palatal tremor and pendular nystagmus in oculopalatal tremor, (e) that a unilateral midbrain lesion can cause a bidirectional vertical gaze palsy, (f) that saccadic adaptation allows ocular motor learning in Chiari II malformation, (g) how nigrostriatal pathways regulate vestibular reflexes, saccades and smooth pursuit, (h) that in

peripheral sixth nerve palsy, selective central monocular adaptation of innervation to the paretic eye occurs, (i) that neural control adaptively underpins Listing's law, (j) the structural-functional relationship of the subnuclei of the oculomotor nucleus, (k) that unilateral lesions of the superior rectus subnucleus of the third nerve nucleus cause a bilateral upgaze deficit.

1. Barton: Johnston JL, Sharpe JA, Morrow MJ. Paresis of contralateral smooth pursuit and normal vestibular smooth eye movements after unilateral brainstem lesions. *Ann Neurol.* 1992; 31: 495–502: *When I was asked to contribute to this article, I immediately thought of this paper. It is far from his most cited work, which would be the studies of eye movements in aging, Parkinson's disease and Alzheimer's dementia. In fact, it has only been cited ten times. It is quite possible, perhaps more than likely, that you do not know of it. Putting aside the numbers, I still doubt that I can defend it as his most important work in terms of shifting our concepts or changing clinical practice. For me, though, this is the quintessential Sharpe paper. There he is on the author list, sandwiched between two fellows who went on to their own successful academic careers. The study is classic neurology, reporting in great detail on four patients, supplemented with neuroimaging, and establishing the range of pursuit*

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abnormalities that could be found in a complex eye movement pathway with double decussations and an intimate relationship with the neural substrate of the vestibulo-ocular reflex. The brainstem was Jim Sharpe's natural home. He had a great fondness for the vestibular system, and in fact wrote a small monograph on its disorders with Hugh Barber, which I read often in my earlier years when I was learning some neuro-otology to round out my neuro-ophthalmologic training. The figures of this paper are classic Sharpe: the sinusoidal ocular motor traces, the CT scans from the earlier days of neuroimaging, the brainstem diagram with nuclei and pathways that explained it all. The discussion draws heavily on monkey neurophysiology. I don't think he ever did any non-human primate work himself, but he was a keen follower of that literature, as I learned from our journal clubs and the papers we wrote together. This report really illustrates his approach: steeped in neurophysiology, he integrated that knowledge with meticulous clinical observations to clarify the anatomy of human ocular motor systems, particularly in the brainstem.

2. Hershenfeld SA, Sharpe JA. Monocular temporal hemianopia. *Br J Ophthalmol.* 1993; 77: 424–427: Monocular temporal hemianopia was identified in 24 patients. The field of the fellow eye was normal. CT or MRI imaging showed juxtaseptal lesions in 19 patients. Of the 24 patients, fifteen had a pituitary adenoma, two had tuberculum sellae meningioma, two had congenital optic disc dysversion, one had craniopharyngioma, one had low grade glioma (astrocytoma), one had optic neuritis and two cases were functional. Monocular temporal hemianopia may be explained by involvement of the ipsilateral optic nerve close enough to the chiasm to selectively impair conduction in ipsilateral crossing fibres but too anterior to affect the crossing retinal nasal fibres from the contralateral eye. Nasal compression of the proximal intracranial optic nerve ipsilateral to the field defect, where nasal and temporal fibres have begun to separate, is probably responsible. Tumour compression of the prechiasmatic optic nerve before the nasal retinal fibres from one eye have begun to cross into the chiasm could explain monocular hemianopia. Monocular field loss may be caused by a differential mechanical pressure effect due to asymmetric tumour growth, or by differential occlusion of chiasmatic nutrient blood vessels. When temporal hemianopia is identified in only one eye, juxtaseptal lesions such as pituitary adenoma or meningioma are likely responsible. The optic discs may be normal or pale. The presence of a relative afferent pupillary defect with or without optic disc pallor on the side of the monocular field loss signifies compression or demyelination of the optic nerve junction with the chiasm.

3. Johnston JL, Sharpe JA. The initial vestibulo-ocular reflex and its visual enhancement and cancellation in humans. *Exp Brain Res.* 1994; 99: 302–308: The vestibulo-ocular reflex (VOR) stabilizes gaze by generating smooth eye movements that are opposite in direction and nearly equal in amplitude to head motion. The response must be short latency in order to prevent image degradation and had been previously measured to be about 6 to 17 ms in human subjects. Vision enhances the VOR when fixating a stationary target or suppresses vestibular smooth eye movements when tracking a target moving with the head (VOR cancellation). Smooth pursuit may contribute to enhancement and cancellation of the VOR but short latency enhancement and cancellation would provide evidence that fixation and smooth pursuit, and VOR cancellation and smooth pursuit are separate ocular motor systems.

Eye and head movements were recorded in 12 normal subjects using a magnetic search coil technique under 3 conditions: VOR in darkness; visual enhancement of the VOR with an earth-fixed stationary target (VORe); and visual cancellation of the VOR with

tracking of a target coupled to move synchronously with head movement (VORc). The initial VOR was determined from regression lines fit along digitized eye and head position records from 80ms of data points after eye and head positions reached 3 SD above baseline. In darkness, VOR gain for the subject group measured 0.90 (SD 0.14). Group VORe gain increased to 0.95 (SD 0.12). When subjects attempted to fixate a target moving with the head, the initial vestibular smooth eye movement was always opposite in direction to the head movement, taking the eyes off target. However, the group VORc gain decreased to 0.84 (SD 0.16). Further slowing of vestibular smooth eye movements occurred about 128 ms after onset of head movement corresponding to the approximate latency of smooth pursuit in humans. Mean initial VOR latencies ranged from 4 to 13 ms and remained the same regardless of condition.

While initial VOR latencies had been previously recorded in a few human subjects, this study confirmed that the horizontal VOR is subserved by a very short latency pathway which remains the same, even when attempting to track a head-fixed target. We also showed that VOR enhancement in humans can occur prior to the onset of smooth pursuit providing evidence that fixation and pursuit are distinct ocular motor systems; that is, fixation is not simply pursuit of a target at zero velocity. Additionally, initial VOR cancellation was shown to have two time courses. A short-latency cancellation occurred within 80 ms of head movement, prior to the onset of visual-following reflexes. This short-latency cancellation was incomplete and variable, accounting for less than 15% reduction in compensatory eye movements, but providing evidence that pursuit and VOR cancellation are distinct ocular motor systems. Secondary improvement in VOR cancellation occurred after the smooth pursuit system detects retinal slip and provides a supplementary signal to the cancellation system thereby achieving accurate eye-head tracking. This study showed that fixation, smooth pursuit and VOR cancellation are all separate ocular motor systems in humans.

4. Kim JS, Moon SY, Choi KD, Kim JH, Sharpe JA. *Neurology.* 2007; 68: 1128–1135: Oculopalatal tremor (OPT) is characterized by palatal tremor in association with synchronous pendular nystagmus. OPT is a delayed complication of damage to the dentatorubro-olivary pathway (the Guillain-Mollaret triangle) and subsequent hypertrophic olivary degeneration. OPT mostly results from focal lesions involving the dentatorubral circuit in the cerebellum or the central tegmental tract in the brainstem. Previously, it had been suggested that OPT could be classified into lateral and midline forms. In the supposed "lateral" form due to unilateral brainstem or cerebellar lesions, the palatal tremor was described as unilateral or asymmetrical and the pendular nystagmus as vertical and torsional with disparate vertical amplitudes between the eyes. In contrast, the proposed "midline" form due to bilateral lesions shows symmetrical palatal tremor and vertical pendular nystagmus. However, imaging of the inferior olives or neuropathological evidence for this classification had not been provided.

This study determined the patterns of nystagmus and palatal tremor, and their correlation with the asymmetry of inferior olivary changes on MRIs in 22 patients with OPT. Patients mostly showed vertical pendular oscillations of the eyes with varied combinations of torsional and horizontal components. The main findings of this study were that dissociated pendular nystagmus predicted asymmetrical (unilateral) inferior olivary pseudohypertrophy on MRIs with accuracy, but symmetrical pendular nystagmus was associated with either unilateral or bilateral signal changes in the inferior olivary nucleus. Dissociated pendular nystagmus was associated with MR pseudohypertrophy of inferior olivary nucleus on the side of the

eye with a larger vertical amplitude of oscillation. Of note, four patients never developed palatal tremor despite signal changes in the inferior olivary nucleus. OPT resolved in one patient after 20 years and was markedly reduced in another patient after six years.

This study provided the first detailed descriptions of the patterns of palatal tremor and pendular nystagmus, and their correlations with MRI findings in OPT. The patterns of pendular nystagmus were far more complex than those previously described. The various patterns of PN in patients with OPT did not correlate with the laterality of inferior olivary changes on MRI and did not support the prior contention that symmetrical vertical nystagmus indicates bilateral lesions and impaired adaptation of the VOR due to degeneration of the inferior olivary nucleus leads to pendular nystagmus in OPT. Although this study could not provide the definite mechanisms of pendular nystagmus, the findings obtained with clinico-radiologic correlation paved the way for subsequent studies of the mechanisms of OPT.

5. Ranalli PJ, Sharpe JA, Fletcher WA. Palsy of upward and downward saccadic, pursuit, and vestibular movements with a unilateral midbrain lesion: pathophysiologic correlations. *Neurology*. 1988; 38: 114–122: When neuro-ophthalmology fellow Bill Fletcher saw an inpatient with bidirectional vertical gaze palsy from an apparently unilateral midbrain infarct, an opportunity arose to investigate and confirm whether a unilateral lesion could cause such a palsy. Dr Fletcher brought the patient up to the laboratory to carefully record various forms of vertical motility with magnetic search coil oculography. He also had the foresight to ask the patient for advance consent for post-mortem brain examination, which was granted. When the patient died of a cardiovascular event later the same admission, a careful sectioning of the brainstem was carried out during the week the fellowship was transferred to Dr Ranalli.

Upward and downward gaze palsy was measured by a magnetic search coil technique and correlated with neuropathologic findings in a patient with a unilateral midbrain infarct. Oculography demonstrated (1) saccadic palsy above primary position and slow, limited vertical saccades below primary position; (2) low-gain, restricted vertical pursuit; and (3) low-gain, abnormal phase lead, and restricted range of the vertical vestibulo-ocular reflex (VOR). Bidirectional palsy of vertical saccades is attributed to unilateral loss of burst cells in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and interruption of burst cell fibres from the opposite riMLF. Pathways mediating vertical pursuit and integration of the vertical VOR also traversed the infarct, which included the interstitial nucleus of Cajal.

A unilateral midbrain lesion is capable of causing bidirectional vertical gaze palsy.

In addition, by drawing from historical case studies of midbrain infarction associated with vertical gaze palsy, and the careful anatomical/oculographic evidence in this case, along with the assistance of a retired medical illustrator, a series of illustrations of putative pathways for upward and downward saccades, smooth pursuit, and vestibulo-ocular reflex (VOR) was created. These have subsequently been incorporated into several textbooks, in addition to numerous citations of this article itself.

An amusing follow-up: When the article was accepted for publication (after the standard 10 drafts under Dr Sharpe's editorial command), I shared the happy news with a neurosurgical training colleague who was doing combined residency/PhD research at the same facility. He paused and remarked, "So that's all you have to do to get a neurology paper published? A single case report?"

6. Salman MS, Dennis M, Sharpe JA. The cerebellar dysplasia of Chiari II malformation as revealed by eye movements. *Can J Neurol Sci*. 2009; 36: 713–724: Chiari type II malformation (CII) occurs commonly in patients with spina bifida/ meningocele. CII is one of the most prevalent congenital deformities of the hind-brain. Mechanical compression, secondary to the small posterior fossa in CII, on the developing hindbrain in early life has been suggested as an explanation for the deformed cerebellum and brainstem in CII. Many patients with CII have impaired smooth pursuit (SP); however, only a few make inaccurate saccades (S) or have an abnormal vestibulo-ocular reflex (VOR). In contrast, saccadic adaptation (SA) and visual fixation (VF) are normal. In this paper, several types of eye movements and brain MRI findings were correlated to describe the extent to which this chronic developmental deformity impairs the function of the different classes of eye movements and relate them to neuroimaging abnormalities.

Several classes of eye movements (SP, S, VOR, VF, SA) were recorded in 21 patients, aged 8–19 years, with CII and 39 age-matched controls, using an infrared eye tracker. Qualitative and quantitative brain MRI data were correlated with the eye movements in 19 CII patients and 28 controls. Abnormal eye movements were present in 9 patients with CII. A significantly smaller cerebellar volume was present in patients with CII than controls. An expanded midsagittal vermis area was noted in patients with normal eye movements in comparison with controls. However, a smaller (non-expanded) midsagittal vermis area, posterior fossa area and medial cerebellar volumes were seen in patients with abnormal eye movements than CII patients with normal eye movements. The findings suggest that the structural deformity of CII affects cerebellar function differently in those with abnormal eye movements. Vermis expansion, from compression caused by a small posterior fossa in some CII patients, may spare its ocular motor functions.

Recording eye movements in children and adolescents is challenging. Recording four classes of eye movements and performing saccade adaptation experiments in children and adolescents with CII is even more difficult and labour-intensive. This study was the last of a series of carefully designed case-control investigations that used different classes of eye movements to investigate the effects of CII, a congenital cerebellar deformity, on ocular motor functions. Ocular motor function was spared in some patients. In addition, evidence was found that, despite the deformity of CII, ocular motor learning still occurs within the small and dysplastic cerebellum, because saccadic adaptation was achieved even in the patients who had eye movement abnormalities. Furthermore, it was the first study to correlate eye movement findings with neuroimaging data in children and adolescents with CII.

7. White OB, Saint-Cyr JA, Sharpe JA. Ocular motor deficits in Parkinson's disease. I. The horizontal vestibulo-ocular reflex and its regulation. *Brain*. 1983; 106: 555–570; White OB, Saint-Cyr JA, Sharpe JA. Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. *Brain*. 1983; 106: 571–587: Idiopathic Parkinson's disease (PD) is primarily a disease of the basal ganglia with sparing of the brain stem. As such, ocular motility was thought to be relatively spared, including the vestibulo-ocular reflex (VOR), a 3-neuron brainstem arc. We examined eye and head movements in 14 patients and 10 age-matched control participants using magnetic search coil techniques. We utilised 3 vestibular paradigms: VOR in darkness, visually enhanced VOR and visual suppression of the VOR. Saccadic protocols included visually guided saccades to predictable and unpredictable saccades, as well as saccades to remembered targets. Smooth pursuit to sinusoidal and ramp targets was studied.

Patients demonstrated low gain VOR in darkness with expected enhancement with a fixed target and paradoxical enhancement during attempted suppression. Saccadic latencies were prolonged. Contrary to previous literature, saccadic velocities were substantially variable with many slow saccades for amplitude. Multistep saccades were frequent and subsequent, corrective saccades to target could be generated at very short latency.

Prior to this study, it was assumed that the vestibular reflexes and saccades were unaffected in PD. Previous studies had studied only peak performance of saccades and did not review the variability of performance.

We attributed the VOR abnormalities to disordered long-loop regulation of the vestibular brainstem reflex analogous to disordered long-loop regulation of spinal reflexes. Saccades are defined by the main sequence relationship between peak velocity and amplitude which is normally tightly regulated. The variability of saccadic velocity raises the possibility of co-activation of opposing ocular muscles due to supranuclear dysregulation, as is observed in the periphery. Short latency corrective saccades deny the possibility of visual feedback and suggest either that they are one saccade, interrupted, or that correction occurs on the basis of internal (non-visual) efferent-afferent mismatch, possibly proprioceptive. Smooth pursuit gain was reduced at all velocities at all frequencies. This indicates abnormality of the gain element rather than limitation of peak velocities.

Nigrostriatal pathways regulate vestibular reflexes, saccadic and smooth pursuit eye movements.

8. Wong AM, McReelis K, Sharpe JA. Saccade dynamics in peripheral versus central sixth nerve palsies. *Neurology*. 2006; 66: 1390–1398; Sharpe JA, Wong AM, Fouladvand M. Ocular motor nerve palsies: Implications for diagnosis and mechanisms of repair. *Progr Brain Res*. 2008; 171: 59–66: *Neuroplasticity is the ability of the brain to adapt its structure and function in response to both healthy and diseased states throughout life. A major theme of Dr James Sharpe's research was neuroplasticity. Before the 1990s, most studies of ocular motor control focused mainly on the horizontal and vertical dimensions, essentially neglecting the third dimension, ocular torsion. With the advent of high-resolution 3D recordings, it became clear that many central issues of ocular motor control cannot be resolved if one ignores the torsional dimension. Combining his intellectual curiosity and scientific and clinical expertise, Dr Sharpe decided with his team to investigate the 3D mechanisms underlying ocular motor control and the possibility of adaptation in paralytic strabismus. Through a series of quantitative investigations, his team elucidated novel findings, shedding new light on the "classic" laws that govern ocular motor control, including Hering's and Listing's laws.*

In one study, saccade dynamics in patients with central or peripheral sixth nerve palsy were evaluated. Patients with central palsy, both acute and chronic, were found to exhibit slow abducting saccades, consistent with limited regeneration within the brain. However, in patients with peripheral palsy, abducting saccadic speed became normal during the chronic phase despite persistent esotropia, suggesting possible central monocular adaptation of innervation selectively to the paretic eye, a finding not predicted by Hering's law. This study also supported the use of saccadic speed as a criterion to distinguish central from peripheral causes of sixth nerve palsy, which is clinically relevant.

In another study, the effects of fourth and sixth nerve palsy on fixation, saccades, and VOR in 3D were investigated. The findings indicated that neural control plays a vital role in the implementation of Listing's law, and that the neural circuitry underlying Listing's law is adaptive, restoring the law despite a palsied muscle. This study

also provided the first documentation of monocular adaptation of the VOR in humans, suggesting that Hering's time-honoured law is not immutable.

Dr Sharpe was the quintessential clinician-scientist who through curiosity, perseverance, and the meticulous study of patients in clinical practice, made new discoveries that continue to benefit people.

9. Zackon DH, Sharpe JA. Midbrain paresis of horizontal gaze. *Ann Neurol*. 1984; 16: 495–504: *This study documented clinical, electro-oculographic and pathological findings in two patients with neoplastic midbrain lesions and drew important conclusions above midbrain ocular motor pathways.*

The structure-function relationship of the subnuclei of the oculomotor nucleus was confirmed and a triad of ocular motor findings was described for unilateral lesions of the midbrain tegmentum — paresis of adduction in the ipsilateral eye due to involvement of the 3rd nerve nucleus in two patients and the MLF in one patient, paresis of contralateral saccades in the contralateral eye and conjugate paresis of ipsilateral pursuit due to lesions of the descending contralateral saccade pathway and the ipsilateral pursuit pathway within the midbrain tegmentum. The study confirmed that unilateral lesions of the superior rectus subnucleus of the 3rd nerve nucleus cause a bilateral upgaze deficit.

Dr Sharpe's contribution to our understanding of the ocular motor system in man is immense. This paper is only a small representation of his large and important body of work.

## Conclusion

The following may be garnered from this sampling of Dr Sharpe's work:

A double decussating pathway mediates smooth pursuit.

Involvement of the ipsilateral optic nerve just near enough to the chiasm produces monocular temporal hemianopia and a relative afferent pupillary defect ipsilateral to the monocular temporal field loss denotes compression of the optic nerve at its junction with the chiasm.

Fixation, smooth pursuit, and VOR cancellation are separate ocular motor systems.

A clinico-radiologic study elucidated the patterns of palatal tremor and pendular nystagmus in oculopalatal tremor and paved the way for further study of OPT.

A unilateral midbrain lesion can cause a bidirectional vertical gaze palsy. Possible pathways for upward and downward saccades, smooth pursuit, and vestibulo-ocular reflex (VOR) were laid out.

A case-control study of four types of eye movements in Chiari II malformation showed that despite that congenital deformity, ocular motor learning still occurs within the small dysplastic cerebellum because saccadic adaptation occurred even in those with eye movement abnormalities. It was the first study to correlate eye movement findings with neuroimaging data in children and adolescents with CII.

Research in PD showed that and how nigrostriatal pathways regulate vestibular reflexes, saccadic and smooth pursuit eye movements.

In peripheral sixth nerve palsy, selective central monocular adaptation of innervation to the paretic eye was demonstrated. That study supported the use of saccadic speed to differentiate central from peripheral causes of sixth nerve palsy, a clinically applicable finding. In another study, the effects of fourth and sixth nerve palsy on fixation, saccades and VOR indicated that neural control underpins Listing's law and that despite a palsied muscle, the

neural circuitry underlying Listing's law is adaptive. The study also provided the first documentation of monocular adaptation of the VOR in humans.

The structural–functional relationship of the subnuclei of the oculomotor nucleus was confirmed and ocular motor findings were described for unilateral lesions of the midbrain tegmentum. The study also confirmed that unilateral lesions of the superior rectus subnucleus of the third nerve nucleus cause a bilateral upgaze deficit.

Dr Sharpe's original research became established knowledge and was incorporated into textbooks.<sup>1–4</sup>

In 2009, an international symposium in honour of Dr Sharpe, Practical Pearls in Neuro-Ophthalmology, was held at the University of Toronto. After he died, highly deserved encomiums appeared in obituaries in journals.<sup>5–7</sup>

One of his former fellows (OW) summed up the experiences and feelings of many when he wrote: “He was a complex character with whom I became closely involved, both in terms of his science but also in terms of the effect he had on me as a person. Although sometimes forthright to the point of being blunt, he did not have an ounce of malice in his body and in fact cared deeply about every one of his fellows and what they could achieve and make of themselves, more so than what they could do for him. He was a great mentor, both scientifically and in terms of teaching how to be a mensch.”

By highlighting a fraction of his vast academic production, we hope we have fittingly honoured Dr Sharpe's memory.

**Acknowledgments.** The many other fellows whom Dr. Sharpe trained and with whom he conducted his research are herewith acknowledged.

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**Statement of Authorship.** Conception (FT); design, data collection, manuscript preparation, review of the manuscript, critical appraisal (JJSB, SAH, JJJ, JSK, PJR, MSS, FJT, OBW, AMW, DHZ).

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