Eye (1989) **3,** 816–832

Treacher Collins Prize Essay
The Significance of Nystagmus

NICHOLAS EVANS
Norwich

Introduction

Ophthalmology found the term νμσταγμοσ, like many others, in classical Greece, where it described the head-nodding of the wined and somnolent. It first acquired a neuro-ophthalmological sense in 1822, when it was used by Good[1] to describe 'habitual squinting'. Since then its meaning has been refined, and much has been learned about the circumstances in which the eye oscillates, the components of nystagmus, and its neurophysiological, neuroanatomic and neuropathological correlates. It occurs physiologically and pathologically, alone or in conjunction with visual or central nervous system pathology. It takes a variety of different forms, the eyes moving about one or more axis, and may be conjugate or dysjugate. It can be modified to a variable degree by external (visual, gravitational and rotational) and internal (level of awareness and visual intention) influences. Physiologically it occurs in response to relative movement between the eyes and their visual field, incorporating the vestibular response to head movements, and this response is useful in investigating the function of both the sensory and motor components of the visual system. Nystagmus inevitably has an effect on visual function, but though in its pathological forms it impairs vision, physiological nystagmus is a strategy designed to optimise vision. It is not surprising that nystagmus can be an intimidating clinical sign, giving rise to diagnostic difficulty.

The ophthalmologist, neurologist and laboratory neurophysiologist individually approach nystagmus analytically, but to grasp its wider significance their insights must be combined. The range of forms it takes, and the circumstances in which it occurs, must be compared and contrasted in order to understand the relationships between nystagmus of different aetiologies. An approach which is synthetic as well as analytic identifies those features which are common to different types and those that are distinctive, and helps describe the relationship between eye movement and vision in nystagmus.

Nystagmus is not properly a disorder of eye movement, but one of steady fixation, in which the relationship between eye and field is unstable. The essential significance of all types of nystagmus is the disturbance in this relationship between the sensory and motor ends of the visual-oculomotor axis. Optimal visual performance requires stability of the image on the retina, and vision is inevitably affected by nystagmus. Oscillopsia is often the result of eye-field instability in acquired nystagmus, the perceptual centres unable to compensate for the oscillation in their reconstruction of the visual world. This contrasts with congenital and physiological forms of nystagmus, in which oscillopsia does not normally occur. Pathological nystagmus reduces visual function to a level less than the retinostriate pathway's capacity, and physiological nystagmus is a strategy to improve vision in the face of movement of field relative to eye. This eye-field relationship is central to an understanding of the significance of nystagmus.

Nystagmus used to be classified as either motor or sensory.[2] Motor and sensory functions are mutually dependent and indivisible in relation to fixation, however, since vision

Correspondence to: Mr. N Evans, FRCS, FCOphth.

provides the major contribution to the control of eye position, and eye position determines visual input. Division of nystagmus into sensory and motor types is an oversimplification, and it is necessary to examine the interface between the sensory and motor visual systems, nystagmus having consequences for both. The component eye movements of nystagmus will be described, and the nature of normal steady fixation and its control identified. The circumstances in which nystagmus occurs will then be considered, particularly its variation in relation to different aetiology. Information will be drawn from neurophysiological and neuroanatomic descriptions of normal eye movements and pathways, clinical reports of nystagmus and visual disorders, and human and animal laboratory studies. In drawing together information from these sources to understand nystagmus, the function of the normal visual and visumotor system is also illuminated.

Eye Movements and the Components of Nystagmus

The oculomotor system has two kinds of active movement at its disposal, from which all reflex and voluntary fixating, repositioning and following movements are synthesised: the fast (FEM) and the slow (SEM) eye movements (together with a distinct variant of the SEM system producing vergence movements). FEMs, exemplified by saccades, are ballistic, that is the movement is preprogrammed and not continuously monitored and controlled. Its peak velocity is proportional to its amplitude, and vision is suppressed while it takes place. The SEM, exemplified by the smooth pursuit movement, is by contrast designed to maintain constant foveation of a target, and is under visually-controlled monitoring. Its velocity is related to the target velocity, up to a maximum. This relation between eye and target velocity describes the 'gain' characteristics of a supranuclear unit which summates or 'integrates' all the inputs influencing eye movements (frontal cortex, visual cortex and secondary visual pathways, vestibular system and proprioceptors). Velocity-coded information (from retinal image slip, burst cell-generated saccades, and from vestibular neurons signalling head movement), is converted by this 'neural integrator' into positional information, which is fed into the oculomotor nucleii to produce eye movements. The integrator is located in the brainstem reticular formation near to the oculomotor nucleii, and has been placed in either the prepositus and vestibular nucleii,[3] or in the burst cells of the PPRF themselves.[4] The output of such an integrator intrinsically depends on its functional integrity, and it can be analysed according to theories of system-control.

Leak and gain are integrator properties of particular importance in relation to nystagmus. Leak denotes a loss of signal in the transformation from velocity to position, and the output of a leaky integrator shows decay—that is the eyes cannot hold an intended new eccentric position, and drift back towards the primary position. This decay shows an exponentially-decreasing time constant, the elastic recoil of the orbital tissues reducing progressively as the eyes approach the midline. A slow movement whose drift from fixation shows exponentially increasing velocity, on the other hand, implies integrator instability with high gain; that is the SEM generator drives the eyes in the direction of the target, under positive-feedback, at increasing velocity, which can exceed that of the target. In both these cases fixation requires a correcting movement after the eyes have moved off-target beyond a critical amount, and this is accomplished by a saccade. If eccentric drift is repeated, refoveating saccades will follow in a cyclical pattern and nystagmus ensues. The origin of nystagmus of any kind, then, lies with the slow eye movement.

Saccades are fed into the ocular motor nucleii from the paramedian pontine reticular formation (PPRF) in the pons, whereas SEMs are probably driven from the Purkinje cells in the cerebellar flocculus.[5] This difference reflects the greater coordination demanded by slow eye movements, which must take into account visual field, head position and movement. Since the two kinds of eye movement arise in separate anatomic locations, they can be involved in disease processes independently of one another, and disorder in one which interferes with accurate foveation can be compensated by a restoring action by the other.

Pathological nystagmus arises when these events alternate in a cycle with appropriate time-characteristics.

It may be stated as a general principle that nystagmus of any sort arises in three circumstances: asymmetric input to the integrator, integrator output which is mismatched with target movement by inappropriately high gain, or integrator leak preventing a fixated target from being held. In addition peripheral disorder (of motor nerve or extraocular muscle) gives rise to nystagmus if the output of the integrator is mismatched with the response of muscle yokes, normal gain being insufficient to maintain steady fixation in the face of progressive effector decay. These classes of nystagmus are examined below in relation to their clinical setting, and the patterns of their component movements shown by eye movement recording.

Vertical eye movements and field organisation differ from those in the horizontal plane in their combination, rather than separation, of lateralised elements of visual field, and anatomically in their more rostral location in the midbrain. There is no evidence that they differ neurophysiologically from horizontal movements, though of course they are involved in different focal lesions in the brainstem, and vertical nystagmus occurs in clinical circumstances separate from horizontal nystagmus.

Steady Fixation

Active SEMs are designed to eliminate movement of the eyes relative to their target. The target may move relative to the observer and the world (signalled by retinal slip), or the observer move relative to the target and the world (signalled by vestibular input). In their pure form these SEMs are then respectively optokinetic smooth pursuit (eyes moving with respect to earth), or a component of the vestibulo-ocular reflex (eye stationary with respect to earth). In both of these the eyes move in the orbits to maintain a stable relationship with the visual field, eye movement velocity being governed by the relative movement of target and subject. Both require constant visual and vestibular input to the SEM generator, the vestibular input being symmetric in the absence of subject movement.

Steady fixation occurs when eye-target relative movement is zero, and can be regarded as a zero-velocity SEM, displaying the characteristic features of other SEMs. Smooth pursuit or VOR intervenes without a break in foveation if head or target should move. Steady fixation requires that the FEM generators on each side are silent, equally suppressed by pause cell discharge. The flocculus, which maintains the eye-field relationship and continuous foveation, has inputs from the visual and prefrontal cortex, superior colliculus, substantia nigra and vestibular nucleii, and, by intracerebellar connection, somatic and extraocular muscle proprioceptors. Of all of these, only the vision-mediated response is a closed loop system (in which the sensor and effector are the same), the others being open loops, capable of less precise control. Because the SEM system is the controller of steady fixation, SEM disorder or lateral bias result in fixation instability, producing nystagmus if accompanied by refixation saccades. Conditions producing nystagmus may be located in the SEM generator itself, or more remotely in its descending inputs. Thus the physiological nystagmus elicited in response to an imposed lateral field bias (optokinetic nystagmus, OKN) reflects an asymmetric descending visual input to the integrator, while nystagmus associated with acute unilateral vestibular disease is caused by unequal vestibular input, and that associated with achromatopsia and albinism may reflect deficiency of closed-loop visual feedback associated with defective image transmission. In the case of albinism a further part may be played by the disordered separation of retinal images into hemifields caused by the abnormal crossing at the chiasm.[6] It is possible that a similar mechanism operates in idiopathic congenital nystagmus,[7] but evidence is difficult to collect, and the idea remains speculative. Lateralised lesions of the labyrinths, and those involving the visual and accessory visual pathways in the brainstem, and cerebellar disease, all produce nystagmus by impairing the steady fixation function of the SEM system.

Both input and integrator are adaptable to altered visual, labyrinthine and neurological conditions, and the visual input is dominant,

as can be demonstrated by arranging experimental conditions such that visual and vestibular demands conflict. Such circumstances include the cancellation of vestibular-driven nystagmus following rotation, by visual fixation when rotation stops. This phenomenon has clinical value in vision testing in the very young infant, in whom persistence of the VOR after rotation ceases indicates serious visual impairment, the infant with normal vision suppressing VOR-mediated nystagmus after one or two beats at the end of rotation.

Disconjugate eye movements

Because the postchiasmic sensory system is organised according to field, and the supranuclear eye movement centres produce conjugate deviations of both eyes, it might be supposed that the visual input is entirely field-coded, and that the motor system produces equal movements of both eyes, in accordance with Hering's law of equal innervation. It is surprising, then, that asymmetric nystagmus is found in association with disorder in both the sensory and the motor ends of the visuomotor system. Violations of Hering's law have been recorded[8] as falling into two categories: dynamic violations, which occur in the absence of pathology, especially in fatigued eyes, and static violations, which only occur in the presence of pathology in the motor control pathways. Asymmetric nystagmus is an example of Hering violation in static oculomotor conditions, and is considered in more detail later.

Nystagmus, then, signifies that the motor control system is unable to maintain steady fixation on account of sustained asymmetry of its inputs, integrator dysfunction, or failure of adaptation, fixation being restored with a FEM when the visual input has sensed the slip away. Similarly, defective visual input may preclude stable fixation, if the image it presents to the motor system is imprecisely organised, or possibly if the two hemifields are incompletely coordinated, preventing the integrator from accurately 'locking on' to an internal representation of the world outside.

Having established the neural basis of steady fixation, and thence the background to nystagmus, the clinical circumstances in which specific types arise can be considered. The significance of an individual case of nystagmus lies in the relation of its features to their clinical setting. It can provide information of diagnostic, localising and therapeutic value, and is useful in the assessment of visual function. It is important to bear in mind the implications of nystagmus on vision in each case, since it is at this level that the disorder has its impact on the subject.

Assessment and Classification of Nystagmus

Nystagmus was formerly divided into pendular and jerk types, reflecting the relative symmetry or asymmetry of its vectors on the one hand, and the limitations of clinical observation on the other. It is generally recognised now that such a classification has little diagnostic or nosologic value, and electronic techniques of eye recording have made possible more detailed classifications according to wave form, which carry implications of mechanism. Nevertheless, few centres are able to undertake electronystagmography, and the initial assessment of a patient with nystagmus is clinical. A classification according to clinical criteria is therefore presented, in Tables I and II.

The examination of a patient with nystagmus must be organised to reveal as much information relating to the nystagmus as possible. It is not appropriate here to discuss aspects of the general medical, neurological and ophthalmic history and examination which may be involved, and the discussion will be confined to consideration of the clinical features of the nystagmus.

History

It is of fundamental importance to establish the onset of nystagmus, so that acquired forms may be distinguished from congenital.[9] The congenital status of nystagmus is a particularly important point to establish when presentation involves neurological signs indicating possible acquired pathology. Many subjects with congenital nystagmus (CN) have family histories suggesting autosomal dominant or sex linked inheritance. Similarly, clues suggesting other disease in the anterior visual pathway, or albinism, should be sought. The effect of nystagmus on the subject's vision is the principal source of symptoms, and oscil-

Table I *Congenital nystagmus (onset within first 4 months)*

Clinical Features	
uniplanar horizontal almost always	
decrease on	convergence
	voluntary lid closure
	dark
	gaze to null zone
	mental distraction
increase on	fixation
	mental concentration
abnormal	OKN ("reversal")
	pursuit
waveform	exponentially increasing slow phase
associated	abnormal head posture
	abnormal head movements
without associated visual pathway disorder (idiopathic)	
Manifest (MN)	
Latent (LN)	revealed on occlusion
	acuity drop on occlusion
	often decreased if optical fogging replaces occlusion
	fast phase of occluded eye always towards fixating eye.
Manifest Latent (MLN)	manifest without occlusion
	on occlusion covered eye nystagmus toward seeing eye.
	amblyopic eye commonly nystagmus towards better eye—? simulation of occlusion
	small amplitude manifest component
associated with other visual pathway disorders:	
albinism, achromatopsia, cataract, optic nerve hypoplasia, tapetoretinal degenerations, retinal dystrophy and detachment, glioma.	
onset delayed until secondary visual system development	
absent in cortical blindness	
unstructured "roving" movements imply profound visual disability	
higher frequencies suggest relatively better visual function	
unilateral optic nerve/chiasm pathology associated with lateralised nystagmus	
specifically localised intracranial lesions associated with characteristic nystagmus patterns, *cf* acquired nystagmus	

Table II *Acquired nystagmus*

vestibular	labyrinthine
	nuclear
central	gaze evoked
	ataxic
	toxic, drug induced and metabolic
mixed	Bruns
specific acquired nystagmus syndromes	

lopsia or other visual change, and its variation with time, head movement, gaze position, illumination and fixation should be noted. These variables all have effects upon specific sites in the motor pathway, and in characterising the nystagmus may help localise its source.

Clinical Examination

Clinical examination reveals the 'direction' of nystagmus (conventionally the direction of its fast phase), and gives a subjective idea of its relative velocity and amplitude (together termed 'intensity') in different positions of gaze. This examination provides information which is often sufficient to characterise the pattern of nystagmus and suggest its neuropathologic basis, and it is easily recorded. The vectors are recorded in the primary position, in the six cardinal positions, and in midline elevation and depression, amplitude being represented by the number of shafts to the arrow or its thickness, and frequency of oscillation by the number of tails (Fig. 1). This simple standard notation permits ready recording of the features of nystagmus, for comparison and future reference, as well as compelling the examining clinician to study the pattern of oscillation carefully. Additional note should be made of any variation on convergence, fixation and lid closure, both voluntary and passive, and of any associated head movements. The response to optokinetic testing, rotation and vestibular stimulation, and FEM and SEM function (to commanded saccades and on smooth pursuit) should be examined. Periodic Alternating Nystagmus (PAN) may have cycles with periods lasting several minutes, a fact that should be remembered in cases demonstrating variability of vector. Finally, the importance of a full eye and neurological examination should not be forgotten.

Eye Movement Recording, Waveforms

The information gained from a clinical examination is usually all that is available to the clinician, and is generally sufficient for clinical management. Objective electronic eye movement recording techniques, however, using DC electro-oculography (EOG)[10] and infra red recording techniques[11,12] have enabled

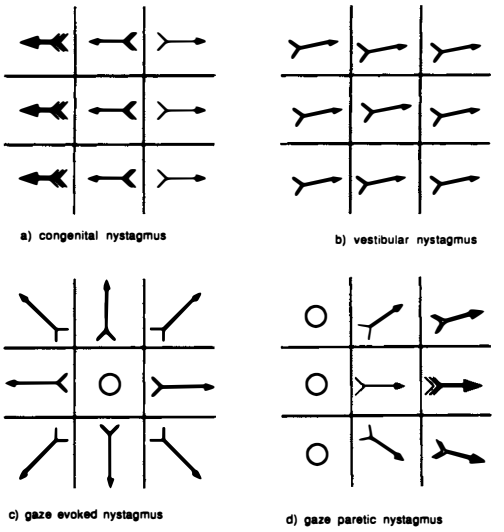

Fig. 1 *Clinical recording of nystagmus*
(a) Congenital nystagmus. High frequency oscillation confined to the horizontal plane, null zone to left of primary position, increasing intensity on opposite gaze.
(b) Vestibular nystagmus. Combination of horizontal and vertical vectors, waveform and intensity uninfluenced by gaze position.
(c) Gaze evoked nystagmus. Nystagmus absent in primary position, increasing on eccentric gaze, with fast phase directed towards gaze position.
(d) Gaze paretic nystagmus. Resolving left gaze paresis, producing nystagmus with maximal intensity on left gaze. The fast phase beats toward the paretic side.

characteristic details of the components of nystagmus to be studied. EOG recording is relatively simple, using standard periocular skin electrodes as for conventional EOG,[13] but recording vertical, torsional and uniocular movements is not satisfactory. For technical reasons, artefact can easily be introduced into the traces, produced by current supply, band-pass characteristics and recording mechanics. Infra red techniques, on the other hand, produce a direct recording of eye movements, are suitable for recording uniocular and multiplanar nystagmus, but require more subject cooperation and greater technical sophistication than EOG. In animal experiments, finally, a search coil may be sutured to the sclera, the electric current induced by eye movement within a magnetic field being recorded directly.[14]

The historic division of nystagmus into pendular and jerk (or saw-tooth) patterns suggests that the motor output in nystagmus has a symmetry which is variable. Electronic recording shows component Slow and Fast eye movements, corresponding to off-target drift and refixation, and a pendular pattern implies approximate equality between these opposing components at a given gaze position, the nystagmus often reverting to a jerk pattern on gaze deviation. Truly symmetric pendular nystagmus, with a sinusoidal waveform, is described as one of the variants of congenital nystagmus by Dell'Osso,[15] who stresses however that the majority of examples of nystagmus previously labelled as pendular were misnamed, objective recording confirming slow and fast components. True pendular nystagmus can also occur in the presence of brainstem disease, commonly of demyelinating or cerebrovascular origin. Gresty and coworkers have documented 32 such cases using electrooculographic recording,[16] which are discussed more fully later. Finally, in the non-directional 'roving' or 'searching' nystagmus of those profoundly visually impaired from birth, the eye movements are not structured, and represent a more complete failure to fixate than the structured nystagmus, characterised by cyclical attempted refixation, with which we are presently concerned.

With insights gained from the study of eye movement traces, a more thorough understanding is possible of the interaction between Fast and Slow eye movements in nystagmus, and the nature of the causal disorder can often be deduced. The relationship of eye position to fixation can also be studied,[17] providing clues as to how nystagmus arises, and indicating the different ways in which the relationship between the oculomotor system and the visual field is disturbed.

The fast component represents an attempt to refixate which may be more or less accurate, is generally linear in profile, and is programmed with respect to the perceived visual field, predicted target motion, known eye position and predicted eye motion. Its significance lies in the accuracy with which it restores foveation during the cycle of nystagmus. It may be regarded as the correcting response in nystagmus.

The slow component, on the other hand,

represents the primary driving force of nystagmus and is highly variable. It may have a linear waveform, or one with an increasing or decreasing velocity. The different profiles of the slow phase imply respectively:

1) **Linear.** Constant eccentric driving trend, not derived from the visual system.

2) **Increasing.** Inappropriately high gain in the vision-mediated control loop coordinating eye position and target. The slow component may be interrupted by secondary saccades, which increase available foveation time, implying a compensatory visual input into the nystagmic mechanism in some types of congenital nystagmus.

3) **Decreasing.** Decay in the position signal from the integrator, allowing the eyes to drift back towards the primary position under the influence of mechanical forces, whose strength decreases exponentially with decreasing angle of eccentricity.

Clinically these classes of slow component profile correspond characteristically with (1) nystagmus of vestibular origin, (2) congenital nystagmus, (3) and gaze-evoked or gaze-paretic nystagmus, and examples of eye movement recording traces illustrating them are shown in Figures 2, 3 and 4. The relationship between target position and eye movement indicates the effect on visual function of nystagmus, and the extent to which the FEM and SEM systems are able to serve the requirements of vision, or are driven inappropriately.

Congenital Nystagmus

Congenital nystagmus (CN) is usually first noticed in infancy, but has a wide range of presentation, ranging from two or three months until in some cases early adulthood.[9] It may be seen alone, or in association with other disorders affecting the infant visual system (Table I). This distinction forms the basis of its classical division into sensory and motor types, though there is no evidence to support a different final mechanism, and the terms have little clinical value.

Clinically CN is confined to the horizontal plane regardless of vertical gaze, its waveform and intensity changing with horizontal gaze. Its uniplanality contrasts with most forms of acquired nystagmus, which may superficially resemble CN, but often show vertical or tor-

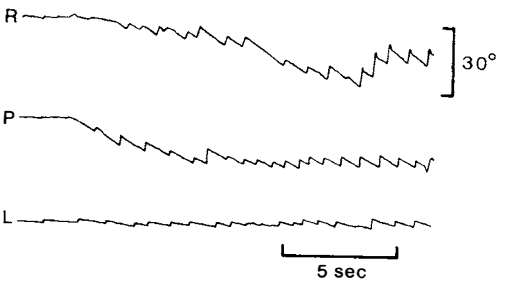

Fig. 2

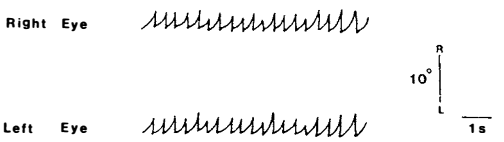

Fig. 3

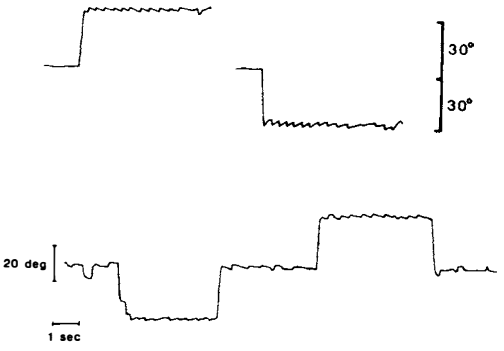

Fig. 4

Fig. 2, 3 and 4 *Electro-oculographic records of nystagmus waveforms.*
Eye movement recordings in vestibular, congenital and gaze evoked nystagmus, showing the pattern of slow and fast eye movements, and the effect of gaze deviation on the direction, frequency, amplitude and waveform. Convention: *upward deflection corresponds to eye movement to right; downward deflection corresponds to eye movement to left.*
(Fig 2) Vestibular nystagmus: Constant velocity slow phase uninfluenced by gaze direction (R = right gaze, P = primary, L = left gaze). Right-beating nystagmus caused by left-sided vestibular pathology.
(Fig 3) Congenital nystagmus: Slow phase shows increasing velocity exponential drift away from fixation (to the right), fast phase regaining fixation. Nystagmus is left-beating and conjugate, ie right and left eye waveforms are identical and in phase.
(Fig 4) Gaze-evoked nystagmus: Decreasing velocity slow phase away from fixation (towards primary position), fast phase towards direction of gaze. Right-beating nystagmus on right gaze, left-beating nystagmus on left gaze.

sional components in positions involving a vertical gaze vector. There are exceptions to this horizontal predilection of CN,[18,19] but these cases are very unusual, and are generally associated with ocular or cerebellar disorder. Intrafamilial studies[20,21] show that there is often a genetic background to CN, though waveform and clinical manifestation are variable amongst related subjects.

Electronic eye movement recording techniques have demonstrated three different classes of waveform in CN, showing pendular, unidirectional jerk and bidirectional jerk patterns. These have been further subdivided into a total of twelve different individual waveforms according to the relationship of the FEM and SEM with foveation.[15,22] These waveform types are shared by subjects with and without associated visual pathway disorder,[17] and differentiation between idiopathic and associated CN cannot be made on the evidence of electronystagmography. Furthermore it is typical of CN that the waveform changes readily from one type to another with variation in gaze position and fixation. Common to all CN waveforms is a characteristic pattern of exponentially increasing velocity deflection away from fixation, interrupted by a linear correcting saccade. This basic pattern may be complicated to a variable degree by superimposed secondary movements, including small breaking and secondary refoveating saccades, and in some cases the identification of waveform requires electronic differentiation of position-time into velocity-time traces. The significance of the waveforms recorded by electronystagmography is that they suggest the kind of neural dysfunction underlying the nystagmus, and describe the relationship between eye position and foveation.

The division into twelve different waveforms may have limited practical clinical significance, but the constant finding of a slow component with exponentially increasing velocity indicates a common mechanism. The increasing velocity is caused by high gain instability in the integrator,—that is the SEM generator drives the eyes eccentrically, under positive feedback, at faster than the target velocity. Whether the integrator itself (which is perhaps no more a neuroanatomic locus than a theoretical construction), or its input, is ultimately responsible, cannot be inferred from examination of eye movement traces. The similarities between idiopathic and associated CN suggests that defective visually-based monitoring of eye movement position plays a part in both, but speculation that subjects with idiopathic CN may have an occult visual sensory disorder, for example subclinical albinism,[7] have not been conclusive.[23,6]

CN occurs in manifest (MN), manifest-latent (MLN) and latent (LN) forms,[24] LN and MLN being associated with strabismus. In LN it seems that the change from binocular (through the 'midline cyclopean eye') to uniocular viewing conditions, on occlusion, produces fixation ambiguity, central projection being an unreconciled conflict between the uniocular single viewing fovea and the binocular 'midline eye', in the presence of heterotropia. Amblyopia, moreover, can simulate occlusion, producing the small amplitude manifest nystagmus in MLN, whose fast phase is directed towards the non-amblyopic eye. Defective pursuit and associated OKN asymmetry are features of strabismic amblyopia[25] as well as of CN. The recognition that MLN has features of both MN and LN suggests a fundamental relationship between all three, and implies that a defect in the coordination of the projections and fields of the two eyes may contribute to the lateral instability. The different OKN responses to temporal-nasal and nasal-temporal stimulation contrast the influence on oculomotor control of the uncrossed nasal fields, which are wholly binocular, with the crossed temporal fields, which are partly uniocular, and it has been suggested that congenital absence of fusion is the reason that MLN is seen in children who have been functionally uniocular from birth.[26] Field separation abnormalities are known to occur in albinism, and the difficulties of registration of the two fields in any disorder involving congenital central visual defect (eg achromatopsia) are evident. It should be remembered, however, that binocular visual function is not incompatible with idiopathic CN on grounds of insufficient acuity alone, since acuity as high as 1.2 is possible in CN.[27] Such acuity implies target foveation lasting at least 100 msec each

cycle.[28] High acuity therefore requires a high degree of coordination between target and fixation, which does not always occur in CN.[17]

Optokinetic Nystagmus (OKN) abnormalities have long been recognised in CN, implicating an SEM defect in its origin. Recent work suggests that the OKN abnormality is not simply an inversion, or an algebraic summation of the optokinetic and congenital components. The variation in the dynamics and waveform of CN with gaze position and on pursuit has already been described. Dell'Osso suggests[28] that the SEM involved in following an OKN stimulus causes a change in the position of the null point, thus altering the direction, and sometimes the waveform, of the underlying CN, so that OKN may appear to be reversed—though in fact it is being shifted. Kestenbaum surgery, and the use of vergence- and version-inducing prisms, similarly have their modifying effect on CN by a manipulation of the null point. The alternating direction of Periodic Alternating Nystagmus (PAN), and the similar, but more labile changes in vector seen in 'bias reversal'[17] probably represent another manifestation of variable null zone effect, on the one hand with stable, and the other with unstable, period.

Kommerell[29] has suggested that an OKN disorder itself may be the cause of CN. In this extension of earlier theories that CN is the result of high gain SEM disorder (subjects with CN are able to track targets with higher velocity than can normals), he proposed that the defect involves failure of coordination between eye position and retinal slip of a moving image, i.e. that the defect is in the OKN system, involving a mismatch between motor output and visual input. This is postulated to be due to a developmental failure of the optokinetic control loop, with partial failure of development producing LN. The increase in intensity of CN during willed visual intention or effort, and its decrease during voluntary (but not passive) lid closure[30] and optical fogging (+30d) or in darkness,[10] confirms that it arises because of disorder of a process in which vision plays a fundamental part. Its modulation by lateral gaze, and the reduction in its intensity during convergence, indicates a disorder involving the version system, and by implication the laterally-separated visual field.

Optican and Zee[31] have developed a mathematical model which explains CN in terms of an inappropriately high positive feedback signal of eye velocity to the integrator. This elegant model works whether the destabilising eye velocity signal is derived from extraocular muscle proprioceptors, or internally, from information on eye velocity within the integrator itself. It also satisfactorily explains the many different waveforms seen in the same subject during different visual conditions. Visual input may then interact with the integrator to produce nystagmus in one of two ways. Either a normal input is processed through a faulty integrator, producing an unstable output, or the tuning of the integrator is defective because of imperfect adaptation in the presence of degraded visual input. This explanation of the mechanism of CN allows as partly correct many previous theories, and emphasises that both motor and sensory factors are simultaneously involved in CN, since the integrator receives interdependent input from both. Similarly the clinical and electronic characteristics of idiopathic and associated CN being indistinguishable, it is likely that an identical mechanism, such as this integrator abnormality, operates in both.

The capacity for exquisite accuracy of saccadic control in CN, which permits accurate momentary foveation during nystagmus, in spite of constant movement of eyes, target and sometimes head, appears to rule out a primary saccadic defect as the cause of CN. Primary cause and its secondary effect may, however, be difficult to distinguish, as was pointed out in a former theory suggesting that a saccade deficit produces CN, the observed high gain in the SEM system being a compensating response.[32]

The relationship between fovea and target not only determines the effect of nystagmus on vision, but also helps explain functional differences between OKN and CN. The relationship between eye position and fixation has been investigated using low light videophotography through an indirect ophthalmoscope, to monitor and correlate the precise foveal position with the target.[17] Optimal foveation strategy in CN requires that the flat portion of the slow phase coincides with target

foveation. These conditions were found in approximately 50% of subjects studied, the remainder failing to coordinate target foveation with that part of the waveform during which eye movement is least. This variable relationship between SEM and foveation accounts for the variability in visual acuity in subjects with CN, and also indicates that the SEM is not a visualising movement as it is in OKN, but that the source of the instability itself is closely related to SEM abnormality.

Acquired Nystagmus (Table II)

Acquired nystagmus signifies acquired disorder in any of the centres or pathways controlling the final input into the oculomotor nucleii. Such disorder results in nystagmus, rather than another supranuclear disorder (for example sustained deviation of conjugate gaze), if inappropriate directional SEM output is cyclically restored by FEM compensation. These centres and pathways may conveniently be divided into those producing:

a) asymmetric tonic input (derived from the labyrinthine and visual systems), into the neural integrator. Nystagmus is characteristically present in the primary position.
b) defective output from the neural integrator (driving the SEM system). Nystagmus is characteristically maximal on eccentric gaze.

Nystagmus produced by these two mechanisms is described respectively as peripheral and central. They are distinguished by slow phases which have respectively linear and exponentially decreasing time courses, reflecting the different mechanisms which produce them.

Aetiological considerations

Acquired nystagmus occurs in association with brainstem, cerebellar or vestibular disease, which the character of the nystagmus may help to localise. The underlying pathology may be focal (glioma, vascular tumour, metastasis) or more diffuse (demyelination, ischaemia, metabolic). CNS depressing drugs are associated with nystagmus, and it is of interest to correlate the effect of diazepam on the integrator, reported as causing a reduction of VOR gain and increase in its time constant,[33] with its clinical effect of gaze-evoked nystagmus. Metabolic disorders associated with nystagmus include Wernicke's encephalopathy[34] and organophosphate poisoning,[35] although conjugate gaze paresis seems to be a more widespread effect on the oculomotor system[36] than nystagmus, perhaps reflecting the symmetric effect on the CNS of metabolic disease.

Peripheral nystagmus

The labyrinths normally supply equal tonic innervation to the vestibular nucleii, the balanced output of which, in the cerebellar flocculus, maintains gaze stability. Lateral bias of vestibular output, caused by head rotation, causes reduction in the SEM generated on that side, the relatively unopposed contralateral SEM generator producing an opposite slow movement which maintains fixation. This is the vestibulo-ocular reflex (VOR), which is normally modulated by concurrent input from the visual system via the corticobulbar and colliculobulbar pathways, and stabilises foveation in the face of head movements. Acute unilateral labyrinthine disorder simulates a VOR, the reduced tonic output of the affected labyrinth leading to an SEM towards the affected side, driven by unopposed tone from the normal labyrinth. This is cyclically interrupted by a refoveating saccade arising from the ipsilateral pontine gaze centres. Peripheral vestibular nystagmus therefore beats away from the side of the lesion, and has linear (constant velocity) slow phases. The intensity of peripheral vestibular nystagmus is reduced by fixation, as visual feedback (via the optokinetic system) overrides the VOR instability. It is characteristic of peripheral vestibular disease that adaptation and recovery occur within a few weeks,[37] the nystagmus generally resolving to leave only abnormal VOR gain responses after 3 months, in spite of persistent deficient vestibular output. Since the disorder does not include the SEM and FEM generators, pursuits and saccades are normal, and since the defect does not include the visual pathway, the pattern of nystagmus is unaffected by gaze position.

It is instructive to compare and contrast the features of vestibular and congenital nystagmus. CN is characteristically horizontally uni-

planar, as has been described, reflecting the organisation of the visual field about a horizontal symmetry. Similarly the plane of peripheral vestibular nystagmus corresponds with the plane of response of the affected vestibular end organs. It is usually predominantly horizontal, with rotatory or vertical components. Pure rotatory or vertical nystagmus cannot have a peripheral vestibular origin[38] because of the labyrinthine geometry. Changes in vestibular nystagmus in response to vestibular stimulation[39] are analogous to changes seen in CN in response to manipulation of visual input. Though vestibular nystagmus is more complex than CN (involving 3 planes), the response to reinforcement of the vector in one plane by rotation or caloric stimulation (termed 'geo-fugal enhancement') is comparable with reinforcement of the vector in CN by lateral gaze, pursuit or optokinetic stimulation. Though the cause of fixation instability is different in vestibular and congenital nystagmus, both occur on a plane whose framework is defined by the sensory input (vestibular and visual) which governs the nystagmus, and each responds analogously to lateral bias in its sensory input.

Lesions affecting the central vestibular pathway produce nystagmus with similar characteristics, though pure vertical and rotatory patterns may be seen, and saccades and pursuits may be impaired, reflecting the higher level of involvement, and greater neural organisation, as well as involvement of adjacent brainstem functions.

Just as peripheral vestibular nystagmus in the horizontal plane can be compared with an inappropriately activated VOR, certain idiosyncratic forms of nystagmus can be understood as specific VOR patterns activated pathologically. See-saw nystagmus (elevation and intorsion of one eye accompanied by depression and extorsion of the other) is a cyclical repetition of the ocular response to head tilt, analogous to artificial horizon instrumentation in an aircraft, and while it has a complex pattern, it can be understood as the inappropriate activation of a physiological mechanism. It may be acquired with midbrain or parasellar pathology, can be simulated experimentally by stimulation of the interstitial nucleus of Cajal[40] or the ultricular nerve,[41] and can be congenital. The heterogeneous neural background to see-saw nystagmus confirms that an extended field of the CNS may be involved in the response, and that the localising value of such specific nystagmus forms can be limited. Their significance lies rather in the comparisons which they suggest with physiological eye-movement responses and other forms of nystagmus, and in the insight they provide about normal control of eye position and movement.

Central nystagmus

The second kind of nystagmus associated with acquired neurological disease occurs as a result of failure of the SEM system to sustain a constant tonic output to the motor nucleii. It is generally caused by loss ('leak') of tonic, or 'step' signal, from the neural integrator, but may be simulated by motor neuropathy, neuromuscular junction disorder (e.g. myasthenia) or extraocular muscle disease, which cause progressive attenuation of effector response. The basic defect is, then, a neural output which is progressively inadequate to sustain the intended eye position, permitting drifts toward the midline which are of decreasing velocity, interrupted by refoveating saccades. The paradox in this waveform is that conditions for satisfactory foveation improve progressively as eye position becomes increasingly off-target (though of course the visual intention lies in the saccade, not the SEM).

This form of nystagmus is termed 'gaze-evoked' (GEN), a specific type being gaze paretic (GPN), which is directional, and seen transiently during recovery of a paresis of conjugate gaze. GEN is maximal on eccentric gaze, and GPN is maximal towards the affected side, decreasing on contralateral gaze. The fast phase beats in the direction of gaze, in an attempt to restore fixation, and the intensity increases with gaze towards the fast phase (Alexander's Law). True central GEN occurs as a result of functional disorder in the pontine gaze centre or cerebellar neurons, which may be associated with demyelination, ischaemia or compression. Drug-induced nystagmus (especially caused by anticonvulsants and sedatives) generally takes the form of

GEN, the drugs' membrane-active effect probably underlying the leak in integrator function.

Mixed central/peripheral nystagmus

Cerebellopontine tumours may produce a combination of central and vestibular nystagmus, by causing pontine compression simultaneously with direct vestibular nerve or end-organ damage. On gaze toward the lesion the features are those of GEN (maximum intensity of nystagmus, the fast phase beating toward the lesion, and an exponentially decreasing waveform). On opposite gaze the vestibular (tonic imbalance) type of nystagmus predominates (unidirectional, no increase on lateral gaze, suppression by fixation, and a linear slow phase). This picture is known as Bruns nystagmus,[42] and elegantly demonstrates the separate mechanisms involved in the two classes of acquired nystagmus.

Asymmetric (ataxic or dissociated) nystagmus

Asymmetric and uniocular nystagmus are found in association with disorders of both the sensory and motor parts of the visual/oculomotor system.

Uniocular nystagmus is found in association with uniocular pathology in infants, particularly optic nerve glioma,[43] and asymmetric nystagmus with greater amplitude on the more affected side occurs in optic chiasm glioma.[44] Marked asymmetry, and sometimes unilaterality of nystagmus, is likewise a feature of spasmus nutans, though optic nerve disease should be excluded by computerised tomography.[45] The supranuclear centres generating eye movements seem to be capable of initiating different movements of the two eyes independently, in violation of Hering's law. More surprisingly, sensory information relating to eye side as well as field side must be preserved beyond the chiasm. The significance of this is considered in the discussion of congenital nystagmus and amblyopia.

Nystagmus involving the abducting eye selectively, in association with adduction paresis, is a feature of lesions involving the medial longitudinal fasciculus (MLF). This unilateral form of nystagmus is truly of motor origin, the MLF providing interneuron connection between the VI and III nucleii, and contrasts with the uniocular nystagmus associated with lateralised sensory lesions (of the optic nerve or chiasm). MLF involvement, usually associated with demyelination, produces in the abducting eye a nystagmus which is essentially of the high-gain instability type, the SEM system increasing its gain in an effort to overcome the internuclear adduction paresis of the adducting eye.

Specific Nystagmus Types

Acquired nystagmus usually corresponds broadly with the patterns described above, its form and associated clinical features suggesting its causal pathology. Certain idiosyncratic forms of nystagmus, showing highly characteristic clinical patterns, have acquired descriptive names. Some of these imply well-defined CNS localisation, allowing aetiologic diagnosis on clinical examination alone. Localisation is not always so accurate, however, and their characteristic patterns can often be correlated only loosely with underlying neural mechanism disorder. Though the idiosyncracy of their patterns is intriguing, their study does not contribute greatly to our general understanding of nystagmus and its mechanisms, and they will be mentioned briefly.

Acquired pendular nystagmus

A distinct form of pendular nystagmus occurring with brainstem disease, usually of demyelinating or cerebrovascular origin, has been documented by objective eye movement recording.[16] The nystagmus differs from pendular CN in that its waveform is independent of gaze position. It is variably uniocular or binocular, conjugate or dysjugate, and occurs in a combination of one or more of the three planes of ocular rotation. Concurrent body tremor is common, and oscillopsia invariable. Saccadic and pursuit movements, and optokinetic and vestibulo-ocular reflexes may all be normal. This form of nystagmus is held to represent a distinct entity on account of its unusual constellation of features, and particularly on account of the narrow band of frequencies of its oscillation, the constant vergence deficiency, and internuclear oph-

thalmoplegia (INO) with which it is associated. It is suggested that the underlying lesion involves cells in close relation to the oculomotor nucleii and the vergence system.

Vertical nystagmus

Downbeat and upbeat nystagmus have been classed with vestibular nystagmus as caused by tone imbalance[46] because of the linear time constant of their slow phases. The causal defect is obscure, but probably involves defective balance in the vertical pursuit generators. The defective horizontal pursuits seen in horizontal nystagmus, and its modulation by horizontal gaze movements, have parallels in vertical nystagmus: the slow phase in downbeat nystagmus is dependent on vertical head position, and vertical pursuit movements are impaired.[47] In convergence-retraction nystagmus, attempted downward vertical pursuit, best elicited in response to a downward-moving optokinetic stimulus, causes extraocular muscle co-conduction and produces cyclical retraction and convergence. It occurs in association with midbrain disorder, as does upbeat nystagmus, and the association of convergence-retraction with a downward optokinetic response perhaps reflects the anatomic proximity of the neural substrates of vertical movement and convergence. Downbeat nystagmus, however, is associated with craniocervical junction and cerebellar abnormalities, especially platybasia and the Arnold-Chiari malformation. The difference between other types of vertical nystagmus, which are located with vertical gaze in the midbrain, and the lower brainstem location of downbeat nystagmus, is not clear.

See-saw and Periodic alternating nystagmus, and Spasmus nutans

See-saw nystagmus has already been mentioned as corresponding with a VOR in the sagittal plane of rotation, and may be caused by inappropriate input to the SEM centres from the central vestibular system. Periodic alternating nystagmus has also been described, and the variation with time of its waveform and direction was shown to correspond with a cyclical movement of the null zone, which is itself influenced by the SEM system.

Spasmus nutans is a self-limiting disorder of infants in which nystagmus coexists with an abnormal head posture (AHP) and abnormal head movements, in the absence of other neurological or ocular disorder. The nystagmus may be conjugate or dysjugate, and is sometimes confined to one eye. If dysjugate, the two eyes may share a common pattern with phase-difference, or the two patterns may be dissimilar.[48] The head movements in spasmus nutans are of some interest. Previously thought to be the convergence of the nystagmus movements, producing a net zero movement of the eyes, it is now recognised that head movement reduces the nystagmus by suppression, rather than by neutralising it algebraically. This suppression, which is a strategy to improve vision, is held to be mediated by vestibular stimulation.[49] The reduction in the intensity of nystagmus in spasmus nutans on vestibular stimulation is analogous to the supression of vestibular nystagmus by visual stimuli.

Physiological Nystagmus

Development and adaptive aspects

Physiological nystagmus may be produced in response to visual (OKN) or vestibular (VOR) stimulation. It maximises foveation time when the relative rotation of eyes, head and field would otherwise reduce visual acuity. The forms of pathological nystagmus described above need to be considered in the light of this capability of oculomotor system to produce oscillating eye movements. The present discussion of physiological nystagmus will be confined to certain experimental and developmental aspects of OKN and VOR, which are relevant to an understanding of the interaction of its components.

The optokinetic response maintains a static relationship between fovea and target during movement of the target, using smooth pursuit to lock foveation for as long as the ocular excursion permits, and saccade to recapture a subsequent phase of fixation. The control system is very precise, and being a closed loop (sensor and effector are the same) is readily adaptable. The critical function in the optokinetic response is its gain, or the relationship between the velocity of eye and target. Experiments investigating the plasticity of

this gain in the OKN and VOR systems in monkeys, involving manipulation of retinal image motion (in an optokinetic drum), vestibular input (by unilateral labyrinthectomy) and visual memory (by occipital lobectomy),[50] indicate that the occipital lobe participates in adaptation (gain adjustment) to fast target movement, though at slow speeds subcortical pathways may suffice. Vestibular nystagmus induced by unilateral labyrinthectomy spontaneously disappeared independently of visual or cortical function. This adaptation appears to be a local property of the vestibular-cerebellar axis, though in more physiological circumstances the dominant optokinetic influence doubtless plays a significant role in adaptation. Accurate VOR gain adjustment is vision-dependent, being delayed until vision is restored, and slowly lost after subsequent occipital lobectomy. The circumstances of these experiments are unphysiological, and extrapolation of the results to the normal human must be guarded. They do, however, suggest how vision, the VOR and the optokinetic response are related, emphasising the dominant influence of visual input in the accurate control of reflex ocular movement. Previous experiments had suggested that extracortical pathways can sustain an attenuated OKN,[51] and it seems that the proposed 'two visual systems'[52] may project a dual input, derived from the cortical and extracortical systems, to the motor control centres.

The extent to which oculomotor reflexes, including nystagmus, require a functional geniculostriate system is unresolved. Clinical observation suggests that the onset of congenital nystagmus of any aetiology is delayed until the geniculostriate system is functional, and that cortically blind infants fail to develop nystagmus, in contrast to those with anterior visual pathway pathology.[53] On the other hand OKN has been reported in (older) infants with cortical blindness.[54] The V.OR is developed before geniculostriate maturity, and the one month infant can maintain fixation by a combination of eye and head movements and VOR.[55] The infant's VOR is less accurate than that of adults,[56] probably reflecting the lesser influence of their immature optokinetic response. The optokinetic response takes 5–6 months to develop, probably in parallel with the development of binocular single vision, and shows temporal-nasal asymmetry during its development.[57,58] The delay in development of the smooth pursuit system in infants, during foveal development, may be another reason why the onset of congenital nystagmus is delayed. Following movements are achieved in the interim by a combination of head movements and small saccades,[59] and the accuracy of following improves significantly over the first two months.[60]

Summary

Nystagmus occurs in a very wide range of circumstances, each type showing characteristic clinical, pathological and electrophysiological features, and analogies between them can be identified by comparing and contrasting nystagmus of different kinds. The effect of altered visual and vestibular conditions on nystagmus, and the features of its waveform, indicate the relationship between eye movements and vision, and the influence of visual and vestibular input in stabilising steady fixation. Ultimately, the significance of nystagmus is that it indicates the state of the mechanisms underlying this stabilisation: in physiological nystagmus they are operating successfully, and in pathological nystagmus they are disturbed. More than this, investigation of nystagmus has shown that the visual system is not divided in a clear-cut way into sensory and motor poles, but that between them there exists a neural region where a 'copy' of the visual world is matched with a programme of potential eye movements, and where sensorimotor information exists indivisibly. Long feedback loops, involving occipital cortex and extraocular muscle proprioceptors, and short ones within the cerebellum and integrator, emphasise the great precision involved in eye movement control, enabling the visual cortex to make optimal use of the resolution capabilities of the fovea.

Nystagmus always reflects an asymmetry in the output of the eye movement generators, and it has been shown that the inappropriate movement which is responsible for pathological nystagmus is the slow movement. This

may arise because of an intrinsic defect in that part of the generator called the neural integrator, or because of 'tonic imbalance' in its input.

Nystagmus occurring with identifiable acquired central nervous pathology can, to some extent, be understood mechanistically, but idiopathic congenital nystagmus poses greater difficulties. Analysis of its waveform suggests that an intrinsic fault in the integrator can explain the clinical and electrophysiological findings in CN, but the cause of the high gain instability in the integrator remains to be explained. The integrator is adaptable. or self-tuning, adjusting its output by visual feedback. Circumstantial evidence suggests that the original disorder in idiopathic CN may occur higher than the integrator, detuning it by conveying an inappropriately organised visual input. In particular if the organisation of the visual system into fields is defective, the gaze generators, whose output is orientated according to field, will have a less accurate 'copy' of the world from which to formulate their movements. Defective binocular function is a feature of latent and manifest latent nystagmus, as well as those examples of CN associated with other visual pathway pathology, and the different motor responses to nasal and temporal field stimulation suggest that registration of the two hemifields may play a role in motor coordination. There remain many more mysteries than answers in congenital nystagmus.

Comparisons between different nystagmus types may be made at many levels, indicating that some basic features are common. The relationship between the plane of oscillation and the plane of the eyes and the labyrinths, and their reinforcement in eccentric rotation of gaze, invites comparison between acquired vestibular and congenital nystagmus. Vestibular nystagmus is reduced or cancelled by visual fixation, and nystagmus in spasmus nutans is cancelled by vestibular stimulation. A method of controlling CN involving feedback of information via the VIII nerve has been proposed by Abadi and co-workers,[61] using an audible signal whose frequency depends on the intensity of the nystagmus, as feedback. Though this approach has not found widespread use, it has been reported as producing an 82% reduction in amplitude, and a 34% reduction in frequency.[62]

Nystagmus is, in conclusion, a protean sign. It may signify profound visual disability, but is compatible with high visual acuity. It was formerly classified as of motor or sensory origin, but derives from a part of the brain where the two functons are brought together into one. It may signify serious progressive central nervous disease, but may also occur transiently in infancy, along with head-nodding, and resolve spontaneously. It may be explained in terms of neurophysiology, neuroanatomy, mechanics, mathematics, or cybernetic systems analysis, or it may defy the best efforts of explanation. It will always provide a great clinical challenge, and the multitude of related factors it involves will guarantee that whoever studies nystagmus will learn about much else besides in the process.

I am grateful to the MRC Neuro-Otology Unit at the Institute of Neurology, and to Dr. RV Abadi, Department of Optometry and Vision Sciences, University of Manchester Institute of Science and Technology, for kindly providing the traces of nystagmus recordings reproduced in this paper, and to Beverley Sabberton-Coe for their preparation.

References

[1] Good: The Study of Medicine III, pub unknown, quoted OED.

[2] Cogan DG: Congenital Nystagmus. *Can J Ophthalmol* 1967, **2:** 4–10.

[3] Cannon SC and Robinson DA: The final common integrator is in the prepositus and vestibular nucleii. In Adaptive processes in visual and oculomotor systems. Proc Asolimar conference 1985. Eds Keller EL and Zee DS, Pergamon Press Oxford. 307–311.

[4] Eckmiller R: The transition between promotor eye velocity signals and oculomotor eye position signals in primate brainstem neurons during pursuit. in Adaptive Processes in Visual and Oculomotor Systems. Proc Asolimar conference 1985. Eds Keller EL and Zee DS, Pergamon Press Oxford. 301–5.

[5] Miles FA and Fuller JH: Visual tracking and the primate flocculus. *Science* 1975, **189:** 1000.

[6] The VEP and misrouted pathways in human albinism. In Cracco RQ, Wollner IB Eds. Frontiers of Clinical Neuroscience Series. Evoked Potentials. New York. Alan Liss Inc. 1986: 211–16.

[7] Simon JW, Kandel GL, Krohel GB, Nelsen PT: Albinotic characteristics in congenital nystagmus. *Am J Ophthalmol* 1984, **97:** 320–7.

[8] Bahill AT, Ciuffreda KJ, Kenyon R, Stark L.

Dynamic and static violations of Hering's law of equal innervation. *Am J Optom and Physiol Optics* 1976, **53:** 786–96.

[9] Gresty M, Page N, Barratt H: The differential diagnosis of congenital nystagmus. *J Neurol, Neurosurg Psychiatry* 1984, **47:** 936–42.

[10] Yee RD, Wong EK, Baloh RW, Honrubia V: A study of congenital nystagmus: Waveforms. *Neurology* 1976, **26:** 326–33.

[11] Cook G and Stark L: The Human Eye Movement Mechanism; experiments, modelling and modeltesting. *Arch Ophthalmol* 1968, **79:** 428–36.

[12] Cook G, Stark L, Zuber BL: Horizontal eye movements studied with the on-line computer. *Arch Ophthalmol* 1966, **76:** 589–95.

[13] Dix MR, Hallpike CS, Hood JD. Electronystagmography and its uses in the study of spontaneous nystagmus. *Trans Ophthalmol Soc UK* 1963, **83:** 531–57.

[14] Fuchs AF and Robinson DA: A method for measuring horizontal and vertical eye movement chronically in the monkey. *J Appl Physiol* 1966, **2:** 1068–70.

[15] Dell'Osso LF and Daroff RB: Congenital nystagmus waveforms and foveation strategy. *Doc Ophthalmol* 1975, **39:** 155–82.

[16] Gresty MA, Ell JJ and Findley LJ: Acquired pendular nystagmus: its characteristics, localising value and pathophysiology. *J Neurol, Neurosurg and Psychiatry* 1982, **45:** 431–9.

[17] Abadi RV and Dickinson CM: Waveform characteristics in congenital nystagmus. *Doc Ophthalmol* 1986, **64:** 153–67.

[18] Hoyt CS and Gelbart SS: Vertical Nystagmus in infants with congenital ocular abnormalities. *Ophthalmic Paediatrics Genetics* 1984, **4:** 155–62.

[19] Sogg RL and Hoyt WF: Intermittent vertical nystagmus in a Father and Son. *Arch Ophthalmol* 1962, **68:** 113–5.

[20] Dell'Osso LF, Flynn JT, Daroff RB: Hereditary Congenital Nystagmus: An Intrafamilial Study. *Arch Ophthalmol* 1974, **92:** 366–74.

[21] Spooner SN, Bateman JB, Yee RD: Congenital Nystagmus in identical twins: Discordant Features. *J Pediat Ophthalmol Strabism* 1986, **23:** 115–9.

[22] Dell'Osso LF: Functional Definitions and classifications of congenital nystagmus waveforms. *Ophthalmol Digest* 1976, **38:** 19–27.

[23] Meienberg O, Hemphill G, Rosenberg M, Hoyt WF: Visually evoked response asymmetries in a family with congenital nystagmus. Possible evidence of abnormal visual projections. *Arch Neurol* 1980, **37:** 697–8.

[24] Dell'Osso LF, Schmidt D, Daroff RB: Latent, Manifest Latent and Manifest Nystagmus. *Arch Ophthalmol* 1979, **97:** 1877–85.

[25] Tychsen L, Hurtig RR, Scott WE: Pursuit is impaired but the vestibulo-ocular reflex is normal in infantile strabismus. *Arch Ophthalmol* 1985, **103:** 536–9.

[26] Harcourt B: Aetiology, classification and clinical characteristics of esotropia. In infancy, in Strabismus and Amblyopia. Wenner-Gren International Symposium Series, **49:** London Macmillan. 1988, 23–35.

[27] Kommerell G, Horn R, Bach M: Motion perception in congenital nystagmus. In: Adaptive processes in visual and oculomotor systems. Proc Asolimar conference, Eds Keller EL and Zee DS, Oxford: Pergamon Press 1985, pp 485–91.

[28] Dell'Osso LF. Congenital Nystagmus: Basic aspects. In: Functional Basis of Ocular Motility Disorders. Proc Int Symposium, Stockholm. Eds: Lennerstrand G, Zee DS and Keller EL, Oxford: Pergamon Press 1981. pp 129–38.

[29] Kommerell G and Medhorn E. Is an optokinetic defect the cause of congenital and latent nystagmus? In: Functional Basis of Ocular Motility Disorders. Proc Int Symposium, Stockholm. Eds: Lennerstrand G, Zee DS, Keller EL, Oxford: Pergamon Press 1981. pp 159–70.

[30] Shibasaki H, Yamashita Y, Motomura S: Suppression of congenital nystagmus. *J Neurol, Neurosurg and Psychiat* 1978, **41:** 1078–83.

[31] Optican L and Zee DS: A hypothetical explanation of congenital nystagmus. *Biol Cybern.* 1984, **50:** 119–34.

[32] Dell'Osso LF, Gauthier G, Liberman G, Stark L. Eye movement recording as a diagnostic tool in a case of congenital nystagmus. *Am J Optom and Arch Am Acad Optom.* 1972, **49:** 3–13.

[33] Blair SM and Gavin M: Modifications of vestibulo-ocular reflex induced by diazepam. *Arch Otolaryngol* 1979, **105:** 698–701.

[34] Zak TA and D'Ambrosio FA: Nutritional nystagmus in infants. *J Ped Ophthalmol Strabismus* 1985, **224:** 140–2.

[35] Jay WM, Marcus RW, Jay MS: Primary position upbeat nystagmus with organophosphate poisoning. *J Ped Ophthalmol Strabismus* 1982, **19:** 318–9.

[36] Cogan DG, Chu FC, Reingold MA, Barranger J: Ocular motor signs in some metabolic diseases. *Arch Ophthalmol.* 1981, **99:** 1802–8.

[37] Baloh RW, Honrubia V, Yee RD, Langhofer L, Minser K. Recovery from unilateral peripheral vestibular lesions. In: Adaptive processes in visual and oculomotor systems. Proc Asolimar conference 1985. Eds Keller EL and Zee DS, Pergamon Press Oxford. pp 349–56.

[38] Van Vliet AGM: Nystagmus. *Doc Ophthalmol* 1982, **52:** 435–46.

[39] Gresty MA, Barratt H, Bronstein A, Page N: Clinical Aspects of Otolith-oculomotor relationships. In: Adaptive processes in visual and oculomotor systems. Proc Asolimar conference 1985. Eds Keller EL and Zee DS, Pergamon Press Oxford. pp 357–65.

[40] Westheimer G and Blair SM: The ocular tilt reaction—a brainstem oculomotor routine. *Invest Ophthalmol* 1975, **14:** 883–93.

[41] Suzuki JI, Tokumasu K, Goto K: Eye movements from single utricular nerve stimulation in the cat. *Acta Otolaryngol* 1969, **68:** 350–62.

[42] Baloh RW, Konrad HR, Dirks D, Honrubia V: Cerebellopontine angle tumours: results of quantitative vestibulo-ocular testing. *Arch Neurol.* 1976, **33:** 507–12.

[43] Farmer J and Hoyt CS: Monocular nystagmus in infancy and early childhood. *Am J Ophthalmol* 1984, **98:** 504–9.

[44] Lavery MA, O'Neill JF, Chu F, Martyn LJ: Acquired nystagmus in early childhood: a presenting sign of intracranial tumour. *Ophthalmology* 1984, **91:** 425–35.

[45] Koenig SB, Naidich TP, Zaparackas Z: Optic glioma masquerading as spasmus nutans. *J Ped Ophthalmol Strabismus* 1982, **19:** 20–4.

[46] Daroff R and Dell'Osso LF: Nystagmus—a Contemporary Approach. In: Topics in Neuro-Ophthalmology, Baltimore. ed Thompson HS. Williams and Wilkins. 1979, 286–97.

[47] Halmagyi GM, Rudge P, Gresty MA, Sanders MD: Downbeating nystagmus. A review of 62 cases. *Arch Neurol* 1983, **40:** 777–83.

[48] Weissman BM, Dell'Osso LF, Abel LA, Leigh RJ: Spasmus nutans. A quantitative prospective study. *Arch Ophthalmol* 1987, **105:** 525–8.

[49] Gresty MA and Hamalgyi GM: Head nodding associated with idiopathic congenital nystagmus. In: Cohen B (ed): Vestibular and Oculomotor Physiology: International meeting of the Barany Society. New York, New York Academy of Sciences, 1981. 614–8.

[50] Fetter M, Zee DS, Proctor LR: Effect of lack of vision and of occipital lobectomy upon recovery from unilateral labyrinthectomy in Rhesus monkey. *J Neurophysiol.* 1988, **59:** 394–407.

[51] Wood CC, Spear PD, Braun JJ: Direction-specific deficits in horizontal optokinetic nystagmus following removal of visual cortex in the cat. *Brain Res.* 1973, **60:** 231–7.

[52] Schneider GE: Two visual systems. Brain mechanisms for localisation and discrimination are dissociated by tectal and cortical lesions. *Science* 1969, **163:** 895–902.

[53] Fielder AR and Evans NM: Is the Geniculostriate System a Prerequisite for Nystagmus? *Eye,* 1988, **2:** 628–35.

[54] Van Hof-Duin J and Mohn G: Optokinetic and spontaneous nystagmus in children with neurological disorders. *Behavioural Brain Research* 1983, **10:** 163–75.

[55] Regal DM, Ashmead DH, Salapetek P: The coordination of eye and head movements during early infancy: a selective review. *Behavioural Brain Research* 1983, **10:** 125–32.

[56] Cordero L, Clarke DL, Urrutia JG: Postrotatory nystagmus in the full-term and premature infant. *Int J Pediatric Otorhinolaryn* 1983, **5:** 47–57.

[57] Naegele JR and Held R: The postnatal development of monocular optokinetic nystagmus in infants. *Vision Res* 1982, **22:** 341–6.

[58] Schor CM, Narayan V, Westall C: Postnatal development of optokinetic after nystagmus in human infants. *Vision Research* 1983 **23:** 1643–7.

[59] Roucoux A, Culee C, Roucoux M: Development of fixation and pursuit eye movements in human infants. *Behavioural Brain Research* 1983, **10:** 133–9.

[60] Ruff HA, Lawson KR, Kurtzeberg D, McCarton-Daum C, Vaughan HG: Visual following of moving objects by full-term and pre-term infants. *J Pediatric Psychology* 1982, **7:** 375–86.

[61] Abadi RV, Carden D, Simpson J: A new treatment for congenital nystagmus. *Br J Ophthalmol* 1980, **64:** 2–6.

[62] Ciuffreda KJ, Goldrich SG, Neary C: Use of eye movement auditory feedback in the control of nystagmus. *Am J Optom Physiolog Optics* 1982, **59:** 396–409.