# Neuro-ophthalmology

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Neuro-ophthalmology involves motor, sensory and autonomic functions from the central and peripheral nervous system. Dysfunction of any of these systems can cause a variety of clinical signs, including decreased vision, blindness, abnormal pupillary light reflex (PLR), anisocoria, abnormal eye movements, neurotrophic keratopathy, facial paresis/paralysis, neurogenic keratoconjunctivitis sicca (NKCS) and static strabismus, alone or in association with multifocal neurological/ophthalmic/systemic signs. The first lecture will cover the anatomy, the function with emphasis to the pathways of the neuro-ophthalmology and during the second lecture we will apply this knowledge to clinical cases.

## Neuro-ophthalmic anatomy and function

### Neurosensory retina and optic nerve

In cats and dogs, the retina is histologically divided into 10 layers (Parry, 1953). Nine layers form the neurosensory retina (embryonic derivative of the diencephalon, neuroectoderm) and the tenth and most external layer (on the scleral surface and closest to the choroid) is the supportive retinal pigmented epithelium. The central area of this tenth layer has no pigment to allow tapetum to show through; the other nine layers of the retina are transparent with the exception of the blood vessels.

The nine identifiable layers of the neurosensory retina, from the outer (scleral) surface to the inner (vitreal) surface, comprise: the photoreceptor layer; the external limiting membrane; the external nuclear layer; the external plexiform layer; the internal nuclear layer; the internal plexiform layer; the retinal ganglion cell layer; the nerve fibre layer (NFL); and the internal limiting membrane. The neurosensory retina layers contain seven types of major cells (six neuronal and one glial): the outer retinal photoreceptors (rods and cones), bipolar neurons, horizontal neurons, amacrine cells, retinal ganglion cells (RGCs) and the Müller cells (glial cells). These cells convert light into electrical impulses, which are sent, via the optic nerve, to the visual cortex (to be transformed into images) and to the brainstem to elicit reflex pathways that coordinate pupil size, head, neck, eyeball movements in response to visual stimuli and synchronize the animal's biological clock.

The ganglion cell layer contains the cell bodies of the RGCs. There is a new subgroup of RGCs identified called melanopsin-containing RGCs (intrinsically photosensitive RGCs (ipRGCs)) that are also photosensitive with melanopsin as the photosensitive pigment. This subgroup of RGCs can respond to changes in light without the input of the outer photoreceptors (cones and rods) and contribute to the regulation of circadian behaviour, seasonal reproductive rhythm and to the PLR.

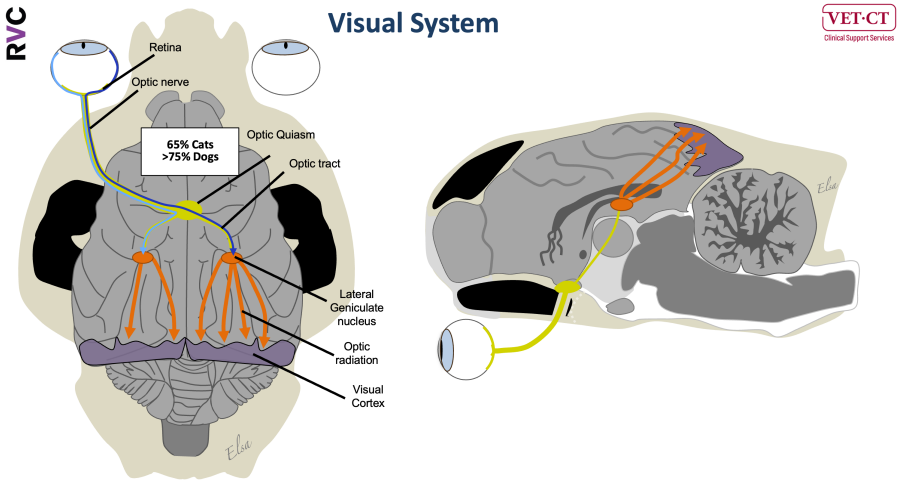
The area in the retina with the highest number of photoreceptors and RGCs is called the area centralis (Mowat *et al.*, 2008); this is specialized for high resolution with maximal visual acuity, comparable to the human macula.

The NFL is mainly formed by axons of the RGCs, which course on the vitreal surface of the retina to the optic disc (optic nerve head or optic papilla) and this point is the origin of the optic nerve (cranial nerve (CN) II). Myelination starts at different levels across the species, which account for the different shapes, colours and position between cats and dogs.

The optic nerve is a white matter tract formed by RGC axons and glial cells. Optic nerve is a misnomer, as a nerve involves a bundle of axons in the peripheral nervous system (PNS) and is myelinated by Schwann cells; however, the optic nerve is a tract of the central nervous system (CNS) and is myelinated by oligodendrocytes. After the lamina cribrosa, the optic nerve is surrounded by meninges (dura mater, arachnoid membrane and pia mater) with a cerebrospinal fluid (CSF) filled subarachnoid space. The RGC axons in the optic nerve are arranged in a retinotopic manner to maintain the spatial arrangement of the retina. The RGC axons course caudally and enter the skull through the optic canals, located in the presphenoid bone at the level of the rostral cranial fossa, to merge into the optic chiasm. The presphenoid bone in the cat but not in the dog contains a sinus (known as the presphenoid sinus). Lesions at the level of the presphenoid bone (e.g. severe presphenoid sinusitis in a cat) can damage the optic nerve and compromise vision (Beltran *et al*., 2010; Busse *et al*., 2009).

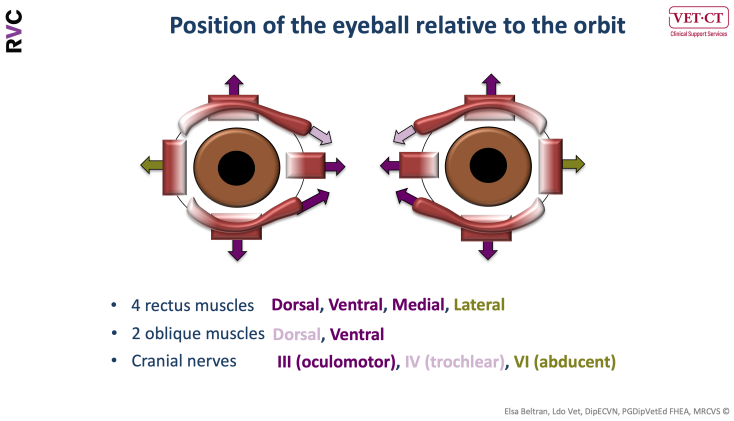
**Chiasm and retrochiasmal pathways to the visual cortex**

The proportion of decussating axons varies between species and correlates with the degree of binocular vision. Species with more binocular fields of view have a smaller percentage of axons crossing at the level of the optic chiasm. Around 66% and 75% of the RGC axons decussate at the optic chiasm in cats and dogs respectively, and the rest remain ipsilateral (around 34% in cats, around 25% in dogs, around 80-90% in horses and cows) (Boire *et al*., 1995; Jacqmot *et al*., 2020). The axons that decussate come from the RGCs in the medial aspect of the retina (which provides the lateral field of view), while the ipsilateral axons come from the RGCs in the lateral aspect of the retina (which provides the medial field of view). The optic chiasm is located intracranially on the floor of the rostral cranial fossa (presphenoid bone) and rostral to the pituitary gland. After the optic chiasm, the RGC axons continue as the optic tract and course caudal dorsolateral over the side of the thalamus. The majority of the optic tract axons synapse in the lateral geniculate nucleus (LGN), located caudal dorsolateral in the thalamus. Some of the optic tract axons (including melanopsin-containing RGC axons) leave the optic tract before reaching the LGN to relay information to extracortical nuclei in the brainstem (pretectal nucleus, rostral colliculus, and suprachiasmatic nucleus). The axons from the neuronal cell bodies in the LGN project into the internal capsule and course caudally as the optic radiation to terminate in the visual cortex and produce the visual perception of images (conscious). A recent study identified the Meyer's and Baum's loops in the canine visual pathway (Jacqmot *et al*., 2020). These loops are axons from optic radiation and therefore contribute to the visual system. The axons of Meyer's loop pass near the temporal lobe to project themselves into the occipital cortex. The axons of Baum's loop make a caudomedial path to project at the level of the parietal cortex before reaching the occipital cortex. This is important neuroanatomy that might need to be considered to prevent damage to the visual system when neurosurgical or radiotherapeutic procedures are planned (Jacqmot *et al*., 2020).



**Eye globe position and eye movements**

The eye position in each orbit and their movements depend on the coordination of three CNs (the oculomotor nerve (CN III), trochlear nerve (CN IV) and abducent nerve (CN VI)), their associated extraocular muscles (the dorsal, ventral, lateral and medial rectus muscles, the dorsal and ventral oblique muscles), and the retractor bulbi muscle, the visual system and the vestibular system.




Movement of the head (acceleration-deceleration) induces movement of the endolymph within the semicircular canals, which stimulates the sensory receptors and sends tonic excitatory input towards the CNS by the vestibular division of CN VIII. The axons course through the internal acoustic meatus to reach the components of the central vestibular system at the level of the rostral medulla oblongata. In the central vestibular system, the majority of the vestibular axons project to the vestibular nuclei in the medulla oblongata (brainstem). From these nuclei, axons project to the spinal cord and other parts of the brain. The axons projecting from the vestibular nuclei bilaterally to the motor nuclei of the CNs III, IV, and VI, via the medial longitudinal fasciculus within the brainstem, provide coordinated conjugate ocular movements (both eyes involved) as the head changes position. This pathway is responsible for physiological nystagmus, which preserves image stability on the retina while the head moves, to optimize performance of the visual system. This pathway can be assessed clinically by evaluating the vestibulo-ocular reflex (VOR) (also known as physiological nystagmus).

The somatomotor nucleus of the oculomotor nerve (CN III) is located in the rostral midbrain. The axons of the oculomotor nerve emerge on the ventrolateral side of the midbrain and course rostrally on the floor of the middle cranial fossa and lateral to the pituitary gland to leave the cranial cavity through the orbital fissure. The orbital fissure is a cleft between the presphenoid and basisphenoid bones. After emerging from the orbital fissure, the oculomotor nerve divides into two branches (dorsal and ventral). The dorsal branch supplies the dorsal rectus muscle and the levator palpebrae superioris muscle. The ventral branch supplies the medial and ventral rectus muscles and ventral oblique muscle of the eyeball.

The nucleus of CN IV is located in the caudal and dorsal part of the midbrain. The axons of CN IV course dorsally around the mesencephalic aqueduct, decussate and continue on the floor of the middle cranial fossa, lateral to the pituitary gland to leave the cranial cavity through the contralateral orbital fissure and innervate the contralateral dorsal oblique muscle of the eyeball.

The nucleus of the abducent nerve (CN VI), is in the rostral medulla oblongata, ventral to the floor of the fourth ventricle. The axons of the abducent nerve course ventrolateral through the medulla and emerge from the brainstem just lateral to the medulla oblongata and course rostrally on the floor of the middle cranial fossa and lateral to the pituitary gland to leave the cranial cavity through the orbital fissure. The abducent nerve branches in the orbit to innervate the lateral rectus and the retractor bulbi muscles of the eyeball.

**Motor and autonomic nerve supply to the eyelids**

The principal muscle elevating the eyelid under voluntary contraction is the levator palpebral superioris muscle, which is innervated by the oculomotor nerve (CN III). There is a very thin muscle, the levator anguli oculi medialis muscle,

which assists in raising the superior (dorsal, upper) eyelid and it is innervated by the auriculopalpebral branch of the facial nerve (CN VII). The resting tone of the eyelid and eyelashes is supplied by Müller's superior tarsal and the arrectores ciliorum muscles, which are innervated by the sympathetic system (discussed later).

The orbicularis oculi muscle is the principal muscle to close the eyelid, which is innervated by the auriculopalpebral branch of the facial nerve (CN VII). The somatic motor nucleus of the facial nerve is in the rostral medulla oblongata, ventral to the floor of the fourth ventricle. The axons of the facial nerve emerge from the brainstem at the lateral part of the rostral medulla oblongata and course rostral to the vestibulocochlear nerve (CN VIII). These two cranial nerves (CN VII and VIII) exit/enter the cranial cavity within a common sheath of dura mater through the internal acoustic meatus. At the base of the internal acoustic meatus, the facial nerve continues laterally through the facial canal of the petrous temporal bone, opens into the cavity of the middle ear (bulla), and then curves caudoventrally in the caudal wall of the tympanum to exit the skull through the stylomastoid foramen. This caudoventral bend formed by the facial nerve is known as the 'knee' of the facial nerve (geniculum) within the facial canal. After emerging from the stylomastoid foramen, the facial innervates the orbicularis oculi and nasolabialis muscles. There are other branches from the facial nerve that are not discussed during these lectures.

**Sensory nerve supply to the eye and surrounding areas**

The sensory innervation of the eye and surrounding areas of the face involves components of the trigeminal nerve (CN V) through its ophthalmic, maxillary and mandibular branches. The ophthalmic branch is purely sensory; it enters the cranial cavity through the orbital fissure. The ophthalmic branch subdivides into three further branches: the lacrimal nerve (innervates the lacrimal gland), the frontal nerve (innervates the skin of the forehead and upper eyelid) and the nasociliary nerve (innervates the corneal epithelium, the skin of the medial canthus of the eye, the septum and parts of the wall of the nasal cavity).

The maxillary branch is also purely sensory; it enters the skull via the rostral alar foramen, the alar canal and the round foramen, located in the basisphenoid bone (on the external surface of the skull it's known as the rostral alar foramen; on the inner surface it is known as the round foramen). The maxillary branch divides into three further branches: the zygomatic nerve (innervates the inferior eyelid, the lateral canthus of the eye and anastomoses are formed with branches of the lacrimal nerve to also innervate the lacrimal gland), the pterygopalatine nerve (innervates part of the nasal mucosa, mainly in the ventral meatus of the nasal cavity and the hard and soft palate) and the infraorbital nerve that continues in the infraorbital canal (innervates the cheek, superior teeth, alveolar periosteum and gums). The zygomatic nerve is not to be confused with the zygomatic branch of the facial nerve.

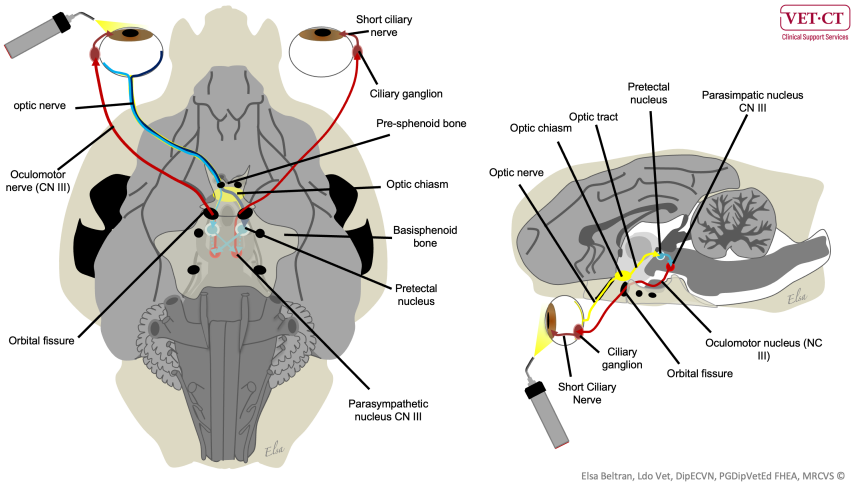
The mandibular branch is sensory and motor (motor component to the muscles of mastication) and it enters/exits the skull via the oval foramen. The sensory part of the mandibular branch innervates the skin of the temporal area, lower mandible and the oral mucous membrane. The axons from the ophthalmic, maxillary and mandibular branches of the trigeminal nerve course from the mentioned receptor organs towards the cranial cavity through the orbital fissure, rostral alar foramen (round foramen internal surface) and oval foramen respectively to reach the trigeminal ganglion, where the cell bodies from these sensory nerves are located. The trigeminal ganglion is located inside the cranial cavity, rostrolateral to the foramen lacerum and in the canal of the trigeminal nerve (rostral part of the petrous portion of the temporal bone). These axons then enter the brainstem at the level of the pons to terminate in the sensory nucleus of spinal tract of the trigeminal nerve, which extends from the pons to the cervical spinal cord segments (SCS). From this nucleus, reflex pathways (such as the corneal reflex and palpebral reflex) and the facial sensation from the innervated areas are processed.

**Autonomic innervation to the eye**

The autonomic innervation to the eye has central and peripheral components, including higher centres in the hypothalamus and midbrain and axons and nuclei in the pons, medulla oblongata and spinal cord. The autonomic system has mainly two components: the general visceral afferent system and the general visceral efferent system with its parasympathetic and sympathetic divisions. The parasympathetic innervation to the eye regulates the iris muscle response (pupil size) to the amount of environmental light, while the sympathetic innervation to the eye regulates the iris muscle response (pupil size) to central factors such as emotion, pain and distress. The iris sphincter muscle is primarily under the control of the parasympathetic nervous system while the iris dilator muscle is primarily under the control of the sympathetic system. Iris muscle constriction (miosis) is produced by contraction of the iris sphincter muscle and relaxation of its antagonist muscle (iris dilator muscle). On the other hand, iris muscle dilatation (mydriasis) is produced by contraction of the iris dilator muscle and relaxation of its antagonist muscle (iris sphincter muscle). This is referred to as reciprocal innervation (Yoshitomi and Ito, 1986). Therefore, pupillary size (under even illumination conditions) is an indicator of the autonomic nervous system tone to the eye.

**Parasympathetic innervation to the eye**

The afferent pathways that contribute to the parasympathetic innervation to the eye arise from the retina, where the impulses originate after light stimulation to the photoreceptors (rods, cones and intrinsically photosensitive RGCs (ipRGCs)). These impulses travel within the RGC axons (optic nerve) and reach the optic chiasm. The majority of the RGC axons decussate at the level of the optic chiasm (around 66% in cats and around 75% in dogs) and continue as part of the optic tract; the rest of the axons remain ipsilateral. Some of the optic tract RGC axons (around 20%) bypass the LGN and course caudally to synapse in the pretectal nucleus (PN) (de Lahunta *et al*., 2021). The PN is located rostrally in the midbrain tectum and contributes to the PLR pathway. From the contralateral PN, the majority of the axons (around 66% in cats and around 75% in dogs) cross over again through the caudal commissure and reach the parasympathetic nucleus of the oculomotor nerve (ipsilateral side to the eye where the light stimulus is given). The parasympathetic oculomotor nucleus (preganglionic nucleus, known as Edinger Westphal nucleus in human neuroanatomy) is located in the rostral part of the midbrain and very close to the midline. The remaining axons from the PN (around 34% in cats and around 25% in dogs) remain ipsilateral to the PN, reaching the contralateral parasympathetic nucleus of the oculomotor nerve to the eye where the light stimulus is given.



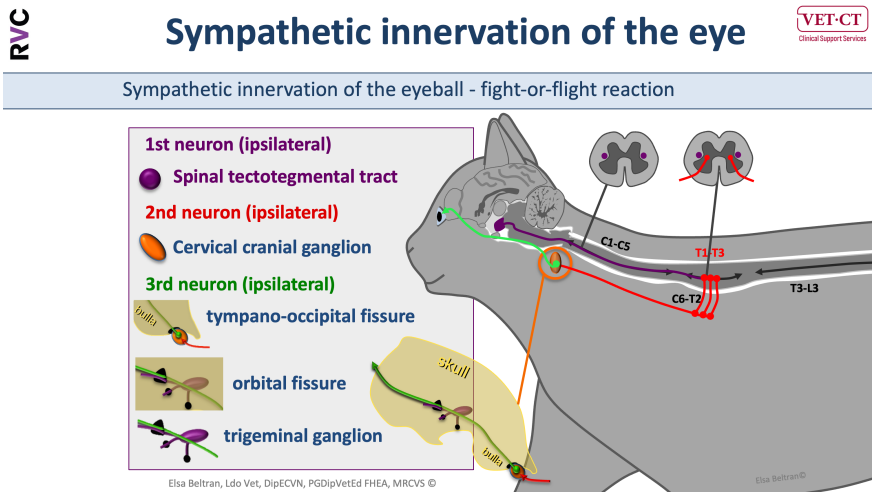

The efferent parasympathetic axons (preganglionic fibres) from the parasympathetic oculomotor nucleus travel with the motor fibres of the oculomotor nerve, coursing ventrally and emerging on the medial side of the crus cerebri. The parasympathetic axons are located medially to the motor fibres of the oculomotor nerve on the floor of the middle cranial fossa and therefore they are the first to be affected when a structural lesion (such as a pituitary gland mass) arises and extends laterally from the midline.

The parasympathetic axons leave the cranial cavity through the orbital fissure and synapse in the ciliary ganglion (postganglionic neuron) caudal and lateral to the eyeball. These postganglionic parasympathetic axons (five

to eight short ciliary nerves in dogs; two short ciliary nerves in cats, nasal (medial) and malar (lateral) nerves) innervate the ciliary body and the iridial sphincter pupillae muscle of the iris to control ocular accommodation and pupil constriction and also give reciprocal cholinergic inhibition to the iridal dilator muscle, causing iridal sphincter contraction and dilator muscle relaxation (pupillary constriction). The reflex in the illuminated eye is considered as the direct PLR, whereas the reflex in the contralateral eye is the indirect, or consensual, PLR.

**Sympathetic innervation to the eye**

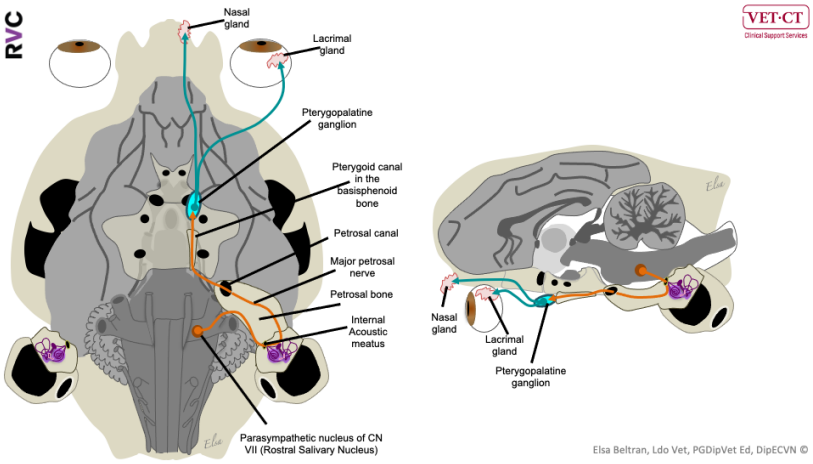
The sympathetic innervation to the eye is described as a three-order neuron pathway. The cell bodies of the first order neurons are in the caudal nuclei of the hypothalamus, which are activated by emotional factors or noxious stimuli. These first order neurons project caudally and ipsilaterally via the lateral tectotegmental spinal tract (located in the brainstem and deep in the lateral funiculus of the spinal cord) to the preganglionic cell bodies (second order neurons), which are in the lateral grey column at the level of T1 to T3 spinal cord segments. The axons from the preganglionic neurons join the ventral roots of the segmental spinal nerves at the same level, emerge through the intervertebral foramina and leave the spinal nerves in the segmental ramus communicans to join the thoracic sympathetic trunk. The preganglionic axons continue cranially as part of the cervical vagosympathetic trunk. This sympathetic trunk is associated with the vagus nerve (CN X) and located in the carotid sheath. At the level of the cranial cervical area and caudomedial to the tympanic bulla, the preganglionic fibres terminate in the cranial cervical ganglion (CCG) where they synapse with the postganglionic neurons (third order neurons). The exact route of these postganglionic axons to reach the smooth muscles of the iris remains undefined. One of the recent reported possible routes describes that the postganglionic axons leave the CCG and course cranially through the tympano-occipital fissure to enter the cranial cavity joining the ophthalmic branch of CN V, coursing on the floor of the middle cranial fossa and emerging through the orbital fissure. The postganglionic sympathetic fibres innervate the smooth muscles of the periorbita, superior and inferior (Müller's) tarsal muscles of the eyelid and the dilator muscles of the iris. The sympathetic input to the dilator muscle causes contraction of this muscle and therefore mydriasis. As previously described in the parasympathetic innervation (see above), the sympathetic innervation also causes a reciprocal inhibition of the other antagonist muscle (iris dilator muscle) and therefore further relaxation of the iris sphincter muscle.




**Autonomic nerve supply of the lacrimal glands**

The autonomic nerve supply of the lacrimal glands originates from the parasympathetic nucleus of the facial nerve (rostral salivary nucleus (RSN)) within the rostral medulla oblongata. The preganglionic parasympathetic axons that arise from the RSN emerge from the medulla oblongata as the intermediate nerve and join the somatic motor axons of the facial nerve before leaving the cranial cavity accompanied by the vestibulocochlear nerve (CN VIII) within a common sheath of dura mater through the internal acoustic meatus. The preganglionic parasympathetic axons of the intermediate nerve leave the main trunk of the facial nerve at the level of the geniculate ganglion (located at the 'knee'

of the facial nerve) in the facial canal of the petrous temporal bone and continue as the greater (major) petrosal nerve (GPN) in the small petrosal canal. The GPN (preganglionic parasympathetic fibres) emerges from the petrosal canal adjacent to foramen lacerum and continues through the pterygoid canal into the pterygoid fossa, where it synapses in the pterygopalatine ganglion on the floor of the orbit where the postganglionic neuron is located. The postganglionic parasympathetic fibres join sensory branches of the ophthalmic nerve (lacrimal nerve) and maxillary nerve (zygomatic nerve) to project to the lacrimal gland. Other postganglionic parasympathetic axons project to glands of the nasal and palatine mucosa,




**Neuro-ophthalmic examination**

The aim of the neuro-ophthalmic examination is to detect whether there are any ophthalmological dysfunctions related to a disorder affecting the nervous system. Neuro-ophthalmic examination begins by taking an accurate history and reviewing any systemic problems that could be relevant. A complete physical, neurological and ophthalmological examination must be performed in any animal with a suspected neuro-ophthalmological disorder.

**Vision**

The pathways of visual perception previously described, and a lesion at any level can cause visual deficits. The clinical assessment of the visual system (in dim and bright light conditions) is mainly performed by observing the animal moving in an unfamiliar environment and negotiating an obstacle course (maze test), and by assessing the menace response. Unilateral visual deficits may be difficult to detect and requires blindfolding each eye in turn.

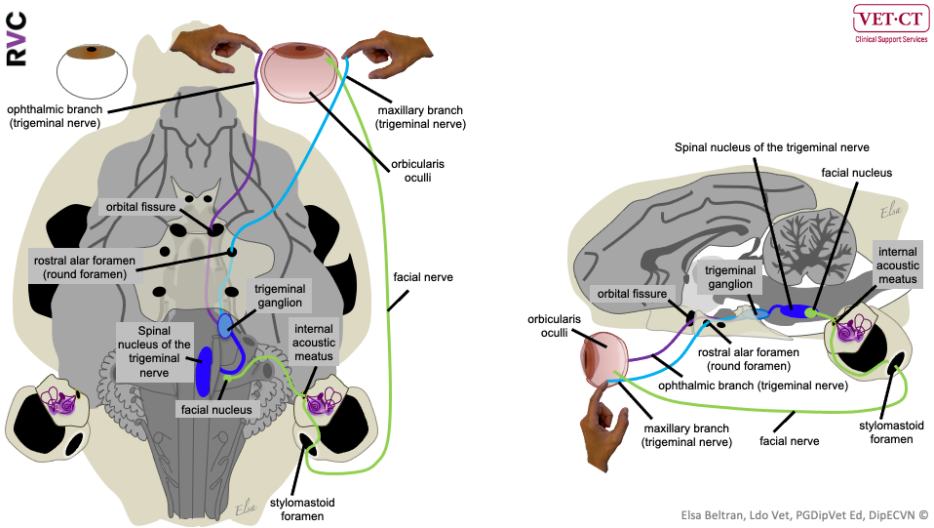
The menace response is elicited by making a threatening gesture to the eye involving the visual fields (medial and lateral) and observing closure of the eyelids. In cats, the most reliable examination mode for the menace response was achieved standing behind the cat (Quitt *et al*., 2019). It is important to avoid touching the eye/eyelashes or creating excessive air currents as this can trigger the palpebral and/or corneal reflex and therefore a false positive menace response. The menace response should also be undertaken in both the medial and the lateral visual fields, when possible, as depending on where the lesion is located, specific types of deficits affecting the visual fields might be present. The menace response requires an intact sensory pathway as previously described (optic nerve, optic chiasm, contralateral optic tract, contralateral LGN, contralateral optic radiation and contralateral visual cortex) and an intact motor pathway to elicit the expected response (closure of the eyelids).

From the visual cortex (mainly from the contralateral occipital cortex) the impulses are transmitted by association fibres to the primary motor cortex (frontal cortex), where the motor pathway of the menace response begins. This pathway has not yet been fully described. The axons from the motor cortex reach the pontine nucleus via projection fibres within the crus cerebri and the longitudinal fibres of the pons. The axons from the pontine nucleus decussate by the transverse fibres of the pons and enter the cerebellum via the middle cerebellar peduncle, reaching the cerebellar cortex, which is ipsilateral to the eye where the menace response is elicited. The cerebellum then coordinates this response by efferent cerebellar pathways that activate the facial nuclei in the ventrolateral part of the

rostral medulla oblongata. A recent study has demonstrated, by transsynaptic tracing in mice, that Purkinje cells in the cerebellar cortex project to the cerebellar interpositus nucleus (CIN), which sends projection fibres to the red nuclei in the midbrain (mainly to the red nucleus contralateral to the eye tested) and the red nuclei send projections to the facial nucleus (mainly ipsilateral to the eye tested) in the medulla oblongata. The axons emerge from the medulla oblongata and leave the cranial cavity via the internal acoustic meatus. At the base of the internal acoustic meatus, the facial nerve continues laterally through the facial canal of the petrous temporal bone and then curves caudoventrally in the caudal wall of the tympanum to exit the skull through the stylomastoid foramen. The facial nerve (CN VII) innervates the orbicularis oculi muscle eliciting a blink (menace response) (de Lahunta *et al*., 2021). If the menace response is decreased or absent, the facial nerve needs to be evaluated with the palpebral reflex because facial nerve paresis/paralysis may result in a reduced/absent menace response without involving deficits of visual perception. Cerebellar lesions, particularly lesions affecting the interpositus and lateral cerebellar nuclei, can also result in a lack of ipsilateral menace response without involving a deficit of visual perception; however, other clinical signs of cerebellar dysfunction will also be present. It is important therefore, to understand the difference between vision and the menace response. A dog or a cat can be visual with an absent menace response if there is a dysfunction of the cerebellum and/or facial nerve; however, the menace response is also absent if the cat or dog has absent vision.

The menace response is a learned response and therefore is usually absent during the first 10 to 12 weeks of age in cats and dogs and the first two weeks in horses and cows. It is important to remember that the menace response is a cortically mediated response, which needs to be consciously perceived; therefore, animals that have a decreased level of consciousness, are stressed, lethargic or disorientated may have an abnormal menace response without necessarily having a lesion in the menace response pathway.

**Palpebral reflex**




The palpebral reflex is elicited by separately touching the lateral canthus and medial canthus of the eye, which induces contraction of the orbicularis oculi muscle and therefore a blink. The sensory (afferent) arm of this reflex is mediated by the trigeminal nerve (CN V), (ophthalmic branch (medial canthus) and maxillary branch (lateral canthus)). These axons enter the cranial cavity via the orbital fissure and rostral alar foramen (round foramen) respectively. The cell bodies of these axons are located in the trigeminal ganglion (inside the cranial cavity, outside the CNS). These axons enter the pons as the trigeminal nerve, course through the spinal tract of the trigeminal nerve (in the medulla oblongata) and synapse alongside the spinal nucleus of the trigeminal nerve with the facial nucleus in the rostral medulla oblongata. The axons emerge from the medulla oblongata and leave the cranial cavity via the internal acoustic meatus. At the base of the internal acoustic meatus, the facial nerve continues laterally through the facial canal of the petrous temporal bone and then curves caudoventrally in the caudal wall of the tympanum to exit the skull through the stylomastoid foramen. The motor (efferent) arm of this reflex is mediated by the zygomatic branch (palpebral branches) of the auriculopalpebral nerve, which is a major branch of the facial nerve (CN VII). The blink is the end point of several neuro-

ophthalmological tests (such as the menace response, corneal reflex and dazzle reflex); therefore, the palpebral reflex should be performed before these tests in order to avoid false-negative results. Brachycephalic breeds may have incomplete eyelid (lagophthalmos) closure due to a shallow orbit and prominent eye globe.

**Pupillary light reflex**

The pathways of the PLR, and a lesion at any level of these pathways can cause PLR deficits. The PLR is a subcortical reflex that regulates the pupil size in response to the intensity of light that falls on the retina. This reflex assists in adaptation to various levels of darkness/brightness and is driven by the activation of the photoreceptor rods, cones and melanopsin-containing RCGs, with different degrees of contribution. Qualitative PLR is evaluated by shining a bright light into the eye and assessing the ipsilateral (direct PLR) and the contralateral (indirect or consensual PLR) pupillary constriction. The PLR is present as soon as the eyes are open; however, the PLR may be sluggish until the normal retinal structure has developed (from 6 to 10 weeks old in cats and dogs). The assessment of the consensual PLR is not necessary if the menace response and the direct PLRs are present in both eyes. However, the consensual PLR can be of a great value when assessing the afferent pathways (optic nerve and optic chiasm) in an eye where the posterior segment cannot be visualized, resulting in a direct PLR that cannot then be assessed (such as with severe corneal oedema). A recording system and protocol has been developed in dogs to reliably quantify the PLR; however, further studies are needed to evaluate if quantitative PLR abnormalities can be associated with specific diseases (Whiting *et al*., 2013; Kim *et al*., 2015). Stressful environments and noxious stimulation can result in pupil dilatation (with little effect on the PLR) due to the influence of the locus coeruleus on pupillary control via sympathetic activation and parasympathetic inhibition. The locus coeruleus is a nucleus located at the level of the pons and is involved with physiological and psychological responses to stress and pain. Other factors that may cause the PLR to be reduced/absent include a low intensity light source, iris atrophy, posterior synechiae, and prior topical administration of a mydriatic agent. Severe retinal, optic nerve, optic chiasm or optic tract lesions are necessary to cause an absent PLR, therefore with only mild retina, optic nerve, optic chiasm or optic tract dysfunction, there is loss of vision, but the PLR could be normal.

**Chromatic/colourimetric pupillary light reflex**

Retinal pathology detection may benefit from chromatic PLR (cPLR), which can distinguish between disorders affecting the outer (closer to the scleral surface) photoreceptors (rods and cones) (as seen in sudden acquired retinal degeneration syndrome, SARDS) and the melanopsin-containing RCG (ipRCG) (Grozdanic *et al*., 2007; Grozdanic *et al*., 2013; Yeh *et al*., 2017; Grozdanic *et al*., 2021). This test is performed using a cPLR device (such as Melan-100®; BioMed Vision Technologies, Ames IA, U.S.A.). This cPLR device is based on the principle that ipRCG can be stimulated with strong blue light (wavelength of 420--440 nm (nanometers)) and induce the PLR. A red light (wavelength of 630 nm) stimulates only the photoreceptors to induce the PLR. Optic nerve lesions may have a decreased to absent PLR regardless of the type of light stimulus used for testing. However, if the disease affects only the photoreceptors (such as in SARDS, immune-mediated retinitis or retinal degeneration), the patient presents with an absent or decreased cPLR using red light and an intact cPLR using blue light. Therefore, cPLR may be a useful method for screening patients that present with loss of vision and PLR with normal mental status, to determine whether further diagnostic tests to evaluate the retina (such as electroretinography (ERG)) should be performed.

**Swinging light (flashing) test**

The anatomical pathway of this test follows the same course as the PLR. This test is performed using a bright light into one eye and, after the direct PLR is achieved (pupillary constriction), the light source is quickly pointed to the

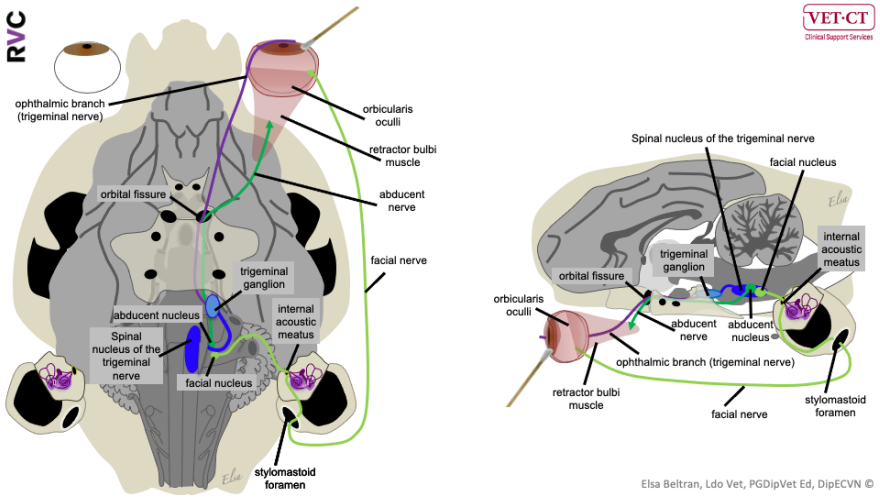
other eye in which further pupillary constriction is expected. The test is then performed in a reversed and repeated manner (swinging movements). A normal reflex is characterized by both pupils constricting to an equal degree when receiving the light stimulus, with the illuminated eye causing further constriction. A mild pupillary escape can be seen when the illuminated eye dilates slightly after an initial contraction; this is a normal reflex, which represents an adaptation of a stimulated retina mainly when using weak light sources. A positive swinging flashing test is considered if the pupil significantly dilates when the light reaches the eye. This pathological pupillary escape (known in humans as Marcus-Gunn sign/pupil) indicates an ipsilateral afferent optic pathway dysfunction (retina or optic nerve).

**Dazzle reflex (photic blink reflex)**

The dazzle reflex is another subcortical reflex induced by stimulating the eye with a very strong light, which causes an eyelid blink. This reflex is present from birth in puppies and kittens. The afferent arm of this reflex is similar to the PLR; however, the efferent arm is mediated via CN VII. Optic tract axons synapse in the rostral colliculus and then tectonuclear axons synapse in the facial nucleus at the level the medulla oblongata to elicit an eyelid blink. This reflex can be useful when the pupils cannot be visualized to evaluate PLR, such as in patients with severe corneal oedema. However, the exact anatomical pathways have not yet been fully elucidated and therefore this reflex cannot be used on its own to localize subcortical lesions.

**Corneal reflex**

This reflex is elicited by gently touching the cornea (avoiding the visual field) with a moistened and sterile stick swab, which results in the retraction of the eye globe (triggered by contraction of the retractor bulbi muscle, innervated by the abducent nerve (CN VI) and an eyelid blink (triggered by contraction of the orbicularis oculi muscle, innervated by the zygomatic branch of the auriculopalpebral nerve, which is a major branch of the facial nerve (CN VII)). Therefore, this reflex requires an intact sensory (afferent) arm (axons of the ophthalmic branch of the trigeminal nerve (CN V), which enters the cranial cavity by the orbital fissure). The cell bodies of these axons are located in the trigeminal ganglion (inside the cranial cavity, outside the CNS). These axons enter the pons as the trigeminal nerve, course through the spinal tract of the trigeminal nerve (in the medulla oblongata) and synapse by the spinal nucleus of the trigeminal nerve with the motor (efferent) arm of this reflex, the abducent nucleus (CN VI) and the facial nucleus (CN VII), in the rostral medulla oblongata. The abducent nerve leaves the cranial cavity through the orbital fissure to innervate the retractor bulbi muscle, which triggers eye retraction. The facial nerve exits the cranial cavity within a common sheath of dura mater with CN VIII through the internal acoustic meatus. At the base of the internal acoustic meatus, the facial nerve continues laterally through the facial canal of the petrous temporal bone, opens into the cavity of the middle ear (bulla) and then curves caudoventrally in the caudal wall of the tympanum to exit the skull through the stylomastoid foramen and innervate the orbicularis oculi, triggering the blink. The sensitivity of the cornea can be quantified by a corneal aesthesiometer, which measures the corneal touch threshold (CTT) (minimum pressure against the cornea to elicit the corneal reflex). The patient should be able to blink to quantify the corneal sensation. A study



has shown major differences in CTT between species, with variable data in the cat (Chan-Ling, 1989; Wieser *et al*., 2013). The regions of the cornea that are less exposed to potential injury (near the eyelid margins) are less sensitive than the central cornea and these regions may elicit a weaker reflex without necessarily being affected by a lesion in the corneal reflex pathway.

**Assessing eyeball movement**

In general, assessing eyeball movement is achieved by:

- Observing the eye movements as the patient looks around voluntarily and in response to induced movements (by holding the head fixed and creating a distraction on either side to see if the animal can appropriately fix its gaze on the visual stimulus in a bilaterally coordinated fashion)
- Assessing the eyes for any asymmetry of the visual axis between the left and right eyes (static strabismus or squint)
- Evaluating the innervation of the retractor bulbi muscles (innervated by the abducent nerve (CN VI)) by observing for retraction of the globe during the corneal reflex (stimulated by touching the cornea, sensation is mediated via the ophthalmic branch of the trigeminal nerve (CN V))
- Retropulsion of the eyeball to assess for the presence of a retrobulbar mass
- Evaluating the vestibulo-ocular reflex (VOR), also known as physiological nystagmus

**Fundic examination**

Fundic examination is an important part of a neuro-ophthalmic examination, and it should be routinely performed in patients with vision loss, anisocoria, or systemic disease (for instance in systemic hypertension, infectious diseases, storage disease or nutritional deficiencies). The fundus includes all the structures in the posterior portion of the eye globe that can be evaluated with the ophthalmoscope (directly or indirectly). Direct ophthalmoscopy provides an upright evaluation of the fundus; however, it provides a highly magnified small field of view, and it might be a difficult technique to use for general screening of the fundus when compared with the indirect ophthalmoscope. There is also a higher risk for the examiner given the proximity to the patient's head. Indirect ophthalmoscopy provides an inverted evaluation of the fundus with a larger field of view but less magnification. It can be performed using a magnifying lens (20—30D (diopter) lens; the less magnification the greater field of view) and a transilluminator without the necessity to use commercial indirect ophthalmoscopes that are expensive.

Veterinary surgeons should be aware of the variations that exist between species or from breed to breed (based on coat colours, age and eye colour) that could contribute to the heterogeneity of the normal appearances of the fundus. For instance, the fundus in young dogs has a bluish colour until the maturation of the retina occurs (usually within the first 3--4 months of life) (Brooks *et al*., 1999). The pupils should be dilated with a sympathomimetic (tropicamide) unless there is any contraindication for its use (such as patients with glaucoma) and the evaluation should take place in a dark/dimly lit room. The structures that routinely need to be evaluated during a neuro-ophthalmic examination of the fundus include:

- Tapetal area -- this contains reflective material (zinc/cysteine) and the non-pigmented epithelial layer, it comprises around 33% of the fundus and it is seen as bright yellow, orange, reddish and green coloured triangular area in the dorsal aspect. Small black or brown spots may be seen at the peripheral tapetum, which could be due to thinning of the tapetum and visualization of the choroidal pigment. This area should be

evaluated mainly for changes in reflectivity and pigmentation. For instance, some inflammatory or degenerative diseases or nutritional deficiencies might show hyperpigmentation

- Non-tapetal area -- this comprises the largest area of the fundus peripherally and ventrally, with dark brown or grey colour due to the retinal pigmented epithelial cells and underlying choroid
- Retinal blood vessels (venules and arterioles) -- there are some variations in the pattern between species and breeds. It is important to evaluate the size of the vasculature and/or the presence of haemorrhages (i.e. hypertensive retinopathy, chorioretinitis)
- Optic nerve head (papilla) -- this represents the axons of the RGC entering the scleral lamina cribrosa where myelination starts. In dogs, myelin extends rostral to the scleral lamina cribrosa and covers the surface of the optic nerve head beyond the scleral canal, giving a circular, triangular or even an irregular shape. In cats the optic nerve head is small, circular and it lacks myelin as the myelination starts at the level of the lamina cribrosa and continues caudally (Brooks *et al*., 1999). The optic nerve head can show some pathological changes including:
    - Papillitis (inflammation of the optic nerve head) -- this can be seen as an oedematous, raised optic nerve head with swollen hyperaemic margins, which can obscure overlying blood vessels with or without peripapillary haemorrhage
    - Papilloedema -- this represents oedema of the optic nerve head due to raised intracranial pressure or optic neuropathy
    - Optic nerve head hypoplasia -- this results in a small optic nerve head with absent/reduced vision likely due to a failure of RGC development
    - Optic nerve head atrophy -- this appears as a flat or cupped optic nerve head with grey colour and attenuation of the blood vessels, which represents an irreversible damage to the RGC, with different possible underlying causes, (e.g. inflammation, ischaemia, chronic compression (for example from chronic glaucoma))

Retinal detachment can also be diagnosed with fundoscopy or, in severe cases, by shining a light into the patient's eye and observing a veil of tissue posterior to the lens. Retinal detachment is a clinical sign with several possible underlying causes, including systemic hypertension, neoplasia, inflammation, infectious disease or even congenital abnormalities.

**Electrophysiological evaluation of the visual system**

Electrophysiological evaluation of the visual system largely comprises electroretinography and visual evoked potentials (VEPs, also called visual evoked responses). It still has a valued role in the era of advanced imaging (magnetic resonance imaging (MRI)/computed tomography (CT)) in both clinical and research neuro-ophthalmology.

**Electroretinography**

Electroretinography (ERG) evaluates retinal function and assesses the retinal cellular responses to a light stimulus. It is useful for the identification of vision loss due to retinal disease including SARDS, or progressive retinal atrophy (Pasmanter and Petersen-Jones, 2020). ERG can be performed under general anaesthesia, or under sedation in a cooperative patient, and it requires the time of dark pupil adaptation (patient placed in a dark room to allow retina to become maximally sensitive to light) as this can affect the ERG results (Lee *et al*., 2009). Conventional ERG recording uses a corneal contact lens electrode, a skin reference and a ground electrode to record retinal voltage changes that occur in response to a defined flash, or repeated flashes, of light. The response is expressed as a waveform, with a-

and b-waves being the most commonly recorded. The waveform and the amplitude and latency of the a- and b-waves are measured. The amplitude of the a-wave and the b-wave increase with the strength of the light stimulus strength, which can be used to evaluate retinal sensitivity. The a- and b-waves are the primary ERG components used for assessing retinal function using conventional ERG. However, other waveforms are recognized and used to evaluate retinal function (Pasmanter and Petersen-Jones, 2020).

**Visual evoked potentials**

VEPs are recordings which arise in response to brief flashes of light. VEPs are recorded using electrodes attached to the scalp and signal averaging techniques. The resulting waveform can be used to assess the function of the central retinal region and post-retinal structures, including the optic nerve, optic chiasm, optic tracts, lateral geniculate nucleus, optic radiation and visual cortex. Obtaining VEPs is largely a research procedure and its use in clinical neuro-ophthalmology is limited, but in generalized CNS disorders the VEP may be used to infer white matter conduction velocity within the CNS by determining conduction velocity within the optic nerve (Maehara *et al*., 2018a; Maehara *et al*., 2018).

**Imaging**

Cross-sectional imaging can provide an excellent complementary diagnostic modality to investigate the dysfunction of the neuro-ophthalmological structures in cats and dogs.

**Orbital ultrasonography**

Optic nerve sheath diameter ultrasonography (ONSD-US) is used in human critical care units to assess intracranial pressure (ICP) and to monitor patients during hospitalization that could develop raised ICP (Koziarz *et al*., 2019). Recent studies in dogs have shown the feasibility of performing this technique and that the measurement of the maximum ONSD-US may provide a noninvasively monitoring tool for evaluation of ICP (Ilie *et al*., 2015; Smith *et al*., 2018). Clinical research is required to further evaluate this technique.

Other visual structures accessible by ultrasound include the extraocular muscles (Penninck *et al*., 2001), which could contribute to the diagnosis of extraocular myopathies in dogs (for instance, extraocular myositis) (Allgoewer *et al*., 2000; Williams, 2008).

**Computed tomography**

CT allows detailed information of the bones of the skull, including the orbit, and sphenoid bones (presphenoid and basisphenoid) to be visualized. This is especially useful in cases with traumatic brain injury affecting the visual pathways.

**Magnetic resonance imaging**

MRI allows investigation of the possible relationship between clinical signs and structural lesions along neuro-ophthalmological pathways. However, prior to interpretation of MRI structural abnormalities, it is important that the MRI appearance of the normal anatomy of the visual pathways and the surrounding structures are well known.

**Cerebrospinal fluid**

CSF analysis could be of diagnostic utility in cases of meningoencephalitis; however, it is unclear of its value in cases of isolated optic neuropathy. The CSF dynamics between the optic nerve subarachnoid space and the CSF is not fully

understood. It is possible that there is a free flow of CSF in the subarachnoid space of the optic nerve, creating an optic nerve compartment syndrome, limiting the value of CSF analysis in these patients (Hao *et al*., 2020).

**Clinical presentation and aetiologies of neuro-ophthalmic disorders**

Once the neuro-ophthalmic examination has been performed, the clinician should be able to further narrow the neurolocalization. We will discuss disorders related to retinopathies, post-retinal visual deficits, neurological causes of strabismus, pathological nystagmus, anisocoria, neurogenic keratoconjunctivitis sicca, neurotrophic keratitis, facial neuropathy and middle cranial fossa syndrome.

**Visual impairment**

Lesions affecting any of the structures involving the visual perception can cause visual deficits: retina, optic nerve (optic neuropathy), optic chiasm, optic tract, LGN, optic radiation and/or visual cortex, either unilaterally or bilaterally. It is important to remember that clear ocular media is required to allow vision; any opacity affecting the cornea, aqueous humour and/or vitreous or lens can contribute to vision loss and therefore these structures should be carefully assessed during the ophthalmological examination.

If visual deficits are present, the PLR is sometimes useful to differentiate between cortical and subcortical lesions. The PLR is present in both eyes if the lesion only affects part of the optic tract, LGN, optic radiation or visual cortex. If there is absent/decreased direct and indirect PLR with post-retinal visual deficits, the lesion is located either in the retina, optic nerve (ipsilateral to the absent direct PLR and visual deficits), optic chiasm (bilaterally absent direct and indirect PLR and visual deficits) or optic tract (contralateral to the absent direct PLR and visual deficits).

**Visual impairment due to retinal diseases**

The signalment, clinical history, ophthalmic examination (particularly of the fundus as tapetal reflectivity could suggest retinal dysfunction as the cause of visual impairment) and ERG are essential in cases with visual deficits to differentiate lesions affecting the retina from post-retinal structures. The most common retinal disorders that may result in visual deficits include:

- Sudden acquired retinal degeneration syndrome (SARDS)
- Progressive retinal atrophy (PRA)
- Retinal pigment epithelial dystrophy
- Retinal detachment
- Retinal toxicity (frequently enrofloxacin in cats and ivermectin in dogs)
- Infectious chorioretinitis
- Immune-mediated retinitis (IMR)
- IMR-cancer-associated retinopathy (CAR)
- Inborn error of metabolism.

**Neurological causes of post-retinal visual deficits**

Lesions affecting any of the structures responsible for visual perception can cause post-retinal visual deficits: optic nerve (optic neuropathy), optic chiasm, optic tract, LGN, optic radiation and/or visual cortex, either unilaterally or bilaterally.

**Optic neuropathy**

Lesions affecting the optic nerve are divided into congenital and acquired lesions. Optic nerve hypoplasia is the most common congenital optic neuropathy. Other congenital abnormalities include optic disc coloboma, usually as part of an ocular syndrome such as the collie eye anomaly, which is beyond the scope of this lecture. Acquired optic neuropathies mainly involve inflammatory/infectious, neoplastic, vascular, compressive, degenerative, traumatic and toxic disorders. An acute onset of visual deficits is usually seen in inflammatory, vascular (mainly ischaemic) and traumatic causes. A chronic course of visual impairment is usually caused by compressive, neoplastic and degenerative disorders.

The main neurological signs of optic neuropathy include visual deficits and decreased/absent direct and consensual PLR. Fundus examination may identify a normal, swollen or pale optic disc, peripapillary vascular attenuation, prominence of the lamina cribrosa, and/or proliferation of neural tissue within/from the optic nerve head. Achieving a definitive diagnosis of an optic neuropathy is challenging given the limited access to the optic nerve and the morbidity associated with biopsy. With a normal fundus examination, advanced imaging provides a vital tool to study structural changes in the optic nerve and hence guide clinical decision making.

**Optic disc/nerve hypoplasia**

Optic nerve hypoplasia (ONH) is primarily documented in dogs, with a high prevalence in Miniature Poodles (Kern and Riis, 1987; Negishi, *et al.,* 2008; Becker *et al.,* 2020), but it also occurs in cats, causing different degrees of visual impairment on the affected eye. It is a non-progressive developmental anomaly characterized by a small optic disc, thinning of the nerve fibre layer and vascular tortuosity, which can be seen on fundus examination. There are several hypotheses for the pathogenesis, including a failure of retinal ganglion cell development and a defect of axon guidance to the CNS. The diagnosis is made based upon fundus examination, decreased to absent PLR and visual impairment. Advanced diagnostic techniques such as *in vivo* imaging of inner retinal microanatomy by spectral domain optical coherence tomography (sdOCT) contribute to the diagnosis in humans, but further studies in veterinary medicine are needed to evaluate their contribution to ONH in cats and dogs (Pilat *et al*., 2015; Occelli *et al*., 2020). There is no treatment, but in those cases with a possible hereditary cause, preventive measures should be taken against breeding.

**Optic neuritis**

Optic neuritis is a form of encephalitis. The inflammation is usually bilateral, but it may be unilateral and affect the entire nerve or just parts of it. Other than inflammation due to compression (see below), there are several underlying causes of optic nerve inflammation, including:

- Immune-mediated disease (Smith *et al.,* 2018; Posporis *et al,* 2019; Bedos *et al*., 2020; Muñiz *et al.*, 2021):
    - Isolated optic neuritis
    - Meningoencephalitis of unknown origin (MUO)
    - Multifocal granulomatous meningoencephalitis (GME)
- Infectious disease (usually presented as multifocal nervous system dysfunction or associated with rhinosinusitis or orbital inflammation) (Gelatt *et al.*, 1973; Stadtbäumer *et al.*, 2004; Baron *et al*., 2011; Richards *et al.,* 2011; Smith *et al.,* 2018; Moghaddam *et al.,* 2020):
    - Viral: canine distemper virus; tick-borne encephalitis; feline infectious peritonitis
    - Fungal: cryptococcosis
    - Protozoal: toxoplasmosis
    - Bacterial: *Escherichia coli* spp.; *Actinomyces* spp.

Differentiating between various underlying causes of optic neuritis requires the use of clinical reasoning and a multidisciplinary approach that goes beyond a clinical history and neuro-ophthalmological examination. Differentiating between the different causes of optic neuritis is important for implementing timely and appropriate treatment. Serology/polymerase chain reaction (PCR) testing, advanced imaging and CSF analysis may help to narrow the list of differential diagnoses.

Optic neuritis is most commonly immune mediated and associated with multifocal MUO, focal GME or isolated optic neuropathy in dogs (Smith *et al.,* 2018). Clinical evidence of feline immune-mediated optic neuritis is currently lacking in the veterinary literature. The median age of presentation for dogs with immune-mediated canine optic neuritis is 4 years old (6 months--11 years), with small-/medium-breed dogs being overrepresented (Smith *et al.*, 2018; Posporis *et al.*, 2019; Bedos *et al*., 2020; Muñiz *et al.*, 2021). The majority of dogs present with an acute onset of bilateral optic neuropathy (70--85%), manifested as absent PLR (60--90%) and visual deficits (Smith *et al.*, 2018; Posporis *et al*., 2019; Bedos *et al*., 2020). Other neurological deficits might be present in cases of multifocal MUO (postural reaction deficits, altered mental status, seizures, central vestibular syndrome). Fundoscopic examination reveals signs consistent with optic neuritis in up to 80% of the affected dogs. MRI features consistent with optic neuritis include enlargement and contrast enhancement of the optic nerve (CN II). Dogs with multifocal MUO might have features of diffuse/multifocal inflammatory disease on MRI. CSF analysis shows abnormalities in up to 60% of the dogs (pleocytosis (mainly lymphocytic/monocytic) with or without increased total protein) (Posporis *et al.*, 2019; Bedos *et al*., 2020).

The treatment protocol for immunosuppressive therapy varies among the literature, however all dogs receive at least corticosteroids and some dogs receive one or more adjunctive immunosuppressive drugs (cytosine arabinoside, cyclosporine, lomustine, azathioprine). Vision recovery occurs in 50% of affected dogs. The presence of a reactive PLR, the absence of fundoscopic lesions, younger age and a lower CSF total cell count at the time of presentation has been associated with vision recovery (Posporis *et al.*, 2019). Further investigation as to whether delaying treatment influences prognosis and the impact this could have on clinical decision-making is required. There is a possibility that the sooner treatment is started the better outcome for vision recovery; however, larger studies are needed to investigate this (Posporis *et al.*, 2019).

**Optic nerve neoplasia**

Primary optic nerve tumours are rare in cats and dogs. Meningiomas and glial cell tumours (astrocytomas, oligodendrogliomas) are the most commonly reported (Mauldin *et al*., 2000; Naranjo *et al.,* 2008; Tvedten *et al*., 2013; Rozov *et al*., 2016) and present as chronic, progressive unilateral visual deficits with decreased/absent direct PLR. An ependymoma arising from the third ventricle mimicking optic neuritis in a dog has been reported (Crawford *et al*., 2019). Lymphoma can affect the optic nerve either by direct extension from the orbit, as primary CNS lymphoma or as metastatic neoplasia (Giordano *et al*., 2013; Nagel *et al*., 2013; Mandara *et al*., 2016). The MRI features of neoplasia of the optic nerve and orbit are variable and depend on the type of tumour. CSF analysis may contribute to the diagnosis in cases of CNS lymphoma (Armour *et al*., 2011). Orbital and optic nerve neoplasia that lack metastasis or do not extend into the intracranial cavity may be treatable with surgical excision, providing a local disease-free interval of more than 1 year in more than 50% of cases; however, recurrence is common (O'Brien *et al*., 1996; Hendrix and Gelatt, 2000; Mauldin *et al*., 2000; Boston, 2010). Prognosis of optic neoplasia in dogs and cats that undergo surgical treatment followed by radiotherapy or chemotherapy still needs to be validated.

**Ischaemic optic neuropathy**

Ischaemic optic neuropathy is a well-recognized differential diagnosis for acute blindness in humans; however, there is limited information in veterinary medicine. A case of ischaemic optic neuropathy that presented with acute bilateral blindness associated with primary systemic hypertension and concurrent cerebrovascular accidents was reported. An ischaemic infarct of the territory supplied by the right internal ophthalmic artery was suspected using MRI (Mari *et al*., 2019).

**Compressive optic neuropathy**

Compressive optic neuropathy can result from infectious, inflammatory, nutritional (vitamin A deficiency) and neoplastic processes affecting the surrounding tissues, including the retrobulbar area and the presphenoid bone (Busse *et al*., 2009; Beltran *et al*., 2010; Schmidt *et al*., 2021). Clinical signs include vision loss and decreased/absent direct PLR. Other cranial nerve deficits can be present if the lesion extends caudally, affecting the cranial nerves that pass through the orbital fissure (CN III, IV, VI, ophthalmic branch of CN V). Advance imaging (MRI or CT) is optimal to diagnose disorders involving the optic nerve and delineate the extent of the lesion. An underlying cause is not found in most dogs and cats with suspected infectious osteomyelitis affecting the sphenoid bones. However, the use of broad-spectrum antibiotics for 3--6 weeks combined with anti-inflammatory medications can be effective and vision might return (Busse *et al*., 2009).

**Traumatic optic neuropathy**

Traumatic optic neuropathy (TON) refers to any damage to the optic nerve secondary to trauma, classified as direct or indirect. Direct TON is caused by a penetrating injury to the area of the optic nerve and usually presents with severe visual loss and minimal possibilities for recovery. Indirect TON is caused by accelerated/decelerated forces due to head/orbital trauma. In these cases, the vision loss could go from mild to total blindness with better chances of recovery, however limited information is available in veterinary medicine. TON has been also reported as a potential complication following enucleation of the contralateral eye, especially in cats where iatrogenic tractional injury at the level of the optic chiasm is suspected (Donaldson *et al*., 2014).

**Toxic optic neuropathy**

Toxic optic neuropathy is characterized by bilateral and symmetrical vision loss caused by a toxin exposure. The optic nerve is susceptible to damage from several toxins, including drugs, metals, organic solvents, methanol and carbon dioxide. The pathophysiology is poorly understood but a possible cause is mitochondrial injury. The prognosis for the recovery of vision depends on the severity of the nerve injury, however some vision might return in the majority of patients after the toxin is discontinued. This type of optic neuropathy is not well described in veterinary medicine and the information is extrapolated from the human literature (Margolin and Shemesh, 2021).

**Optic chiasm lesions**

An optic chiasm lesion can result in bilateral vision loss and bilateral decreased/absent PLRs. The visual loss may present with an acute onset, despite the slow development of the underlying disease process. The optic chiasm is located in the rostral cranial fossa; therefore, intracranial extension of orbital lesions (neoplasia or inflammation), disease of sphenoid bones, traumatic brain injury, CNS diseases (neoplasia, inflammatory or congenital) and tumours of the pituitary area that extend rostrally, can cause damage to the optic chiasm. Lymphoma is a common cause in cats (Chang *et al*., 2006) but consideration should be given to other tumours in both dogs and cats, including pituitary macroadenomas, meningiomas and tumours of the nasal cavity extending into the region of the optic chiasm. An unusual brain tumour called a suprasellar germ cell tumour has been reported in young adult dogs (Cook *et al*., 2018). This tumour expands in the region of the pituitary fossa and can become extremely large, causing compression of the

optic chiasm, and the cranial nerves at the level of the orbital fissure, leading to signs of middle cranial fossa syndrome

**Neurological causes of post-retinal visual deficits: optic tract, lateral geniculate nucleus lesions, optic radiation and visual cortex**

Infectious diseases, in particular canine distemper virus, can cause demyelination of both optic tracts and therefore vision loss (Summers and Appel, 1987). Lesions (vascular, inflammatory, infectious, trauma, congenital, metabolic and neoplastic) in the thalamic area can also affect the optic tracts and LGN. Unilateral lesions will cause contralateral vision loss. It is important to remember that if the lesion affects the rostral part of the optic tract, the PLR could also be affected. The neuronal cell bodies in the LGN and the visual cortex are particularly vulnerable to storage diseases (degenerative), developmental abnormalities, vitamin B1 (thiamine) deficiency and hypoxia.

Vision loss (temporary and permanent) has been reported in cats following general anaesthesia and usually after the mouth has been held open by a gag during an oral procedure. The maxillary artery is the major supplier of oxygen to the feline brain and, when the mouth is held maximally open, the blood flow in this artery can be decreased leading to brain hypoxia (Barton-Lamb *et al*., 2013). It is strongly recommended to minimize the time taken to perform procedures in cats where wide mouth opening is necessary. The visual cortex appears to have an increased sensitivity to hypoxia in cats, so any factors that compromise blood flow to the brain during anaesthesia might lead to brain ischaemia and post-anaesthetic cortical blindness in this species (Stiles *et al*., 2012).

Dogs and cats with thalamic lesions are likely to show other clinical signs in addition to vision loss, including altered mentation/level of consciousness, vestibular dysfunction, abnormal behaviour, circling, postural reaction deficits and seizures. Dogs and cats with cerebral cortex involvement could also present with seizures, decreased consciousness, postural reaction deficits, head turn and hemi-neglect/hemi-inattention syndrome. The hemi-neglect/hemi-inattention syndrome reflects the inability to process and perceive stimuli on the contralateral side of the affected cerebral hemisphere (usually the patient eats from only one half of the bowl, leaving the side that is not perceived by the contralateral cortex in the bowl). Advanced imaging (high field MRI if possible) is best for diagnosing disorders involving the thalamic area and visual cortex and helps delineate the extent of the lesion. CSF analysis may contribute to the diagnosis.

Transient vision loss (cortical blindness) of variable duration after an epileptic event can be present in dogs and cats, although the exact pathophysiology has not been reported. There is no correlation between the severity and the length of the seizures and transient cortical blindness.

**Neurological causes of strabismus, pathological nystagmus and other involuntary eye movements**

**Strabismus and abnormal eyeball movement**

The control of eyeball position and movement involves numerous interconnected neural structures and pathways located in the inner ear, brainstem, cerebellum, basal nuclei and cerebral cortex. Disorders of each of these structures and pathways, as well as lesions involving the extraocular muscles, can cause strabismus and/or eye movement abnormalities.

**Strabismus**

Strabismus is an abnormal position of the eyeball relative to the orbit/palpebral fissure with misalignment of the visual axes (referred to as squint). There are two main types of strabismus caused by neurological dysfunction: positional or vestibular strabismus; and fixed/restrictive or neuromuscular strabismus.

- Vestibular strabismus is a clinical sign of vestibular dysfunction; it is seen when the head and the neck move dorsally and is due to loss of antigravity tone of the eyeball, leading to ventral/ventrolateral deviation of one eye in certain positions of the head (ventrolateral strabismus).
- Neuromuscular strabismus causes the eyeball to be fixed in a deviated position regardless of head position; it can be due to loss of innervation or myopathy of the extraocular muscles. The direction of the neuromuscular strabismus depends on the affected cranial nerve or extraocular muscle(s):
    - Dysfunction of the oculomotor nerve (CN III) results in ventrolateral strabismus or exotropia. A complete CN III lesion (motor and parasympathetic dysfunction) causes areflexive mydriasis (internal ophthalmoplegia), a smaller palpebral fissure due to ptosis, neuromuscular dorsolateral strabismus, and the affected eye will not adduct well on testing physiological nystagmus (vestibulo-ocular reflex) (external ophthalmoparesis). Oculomotor neuropathy has been reported secondary to neoplasia at the level of the middle cranial fossa or orbital fissure and it is usually given a poor prognosis; however, a recent paper described idiopathic canine oculomotor neuropathy (Tetas *et al*., 2017) with good prognosis.
    - Dysfunction of the trochlear nerve (CN IV) results in rotation of the globe (the ventral aspect of the pupil moves dorsomedial). Lesions affecting the trochlear nerve in isolation are extremely rare but, where they do occur, result in loss of function of the ipsilateral dorsal oblique muscle (brainstem lesions may result in ipsilateral or contralateral loss of function). The dorsal oblique muscle functions to rotate the dorsal portion of the globe nasally (intorsion); therefore, lesions of the dorsal oblique muscle are evident upon rotation of the eyeball where the dorsal portion of the eyeball is deviated temporally (laterally). In cats, this is seen as rotation of the normally vertical pupils, but in dogs (which have round pupils) this is only apparent upon demonstrating lateral deviation of the dorsal retinal arteriole and vein on ophthalmoscopic examination.
    - Dysfunction of the abducent nerve (CN VI) results in medial strabismus or esotropia and enophthalmos. Abducent lesions are extremely rare in isolation but, where they do occur, result in medial strabismus of the affected eye (the abducent nerve innervates the lateral rectus and retractor bulbi muscles of the eyeball). Lesions of the abducent nerve can be distinguished from congenital medial strabismus by the absence of eyeball retraction in the affected eye upon performing the corneal reflex.
    - Lesions simultaneously affecting CNs III, IV and VI result in external and internal ophthalmoplegia if the pupillary constrictor (CN III) is affected.
    - Lesions of the extraocular muscles can lead to restrictive strabismus (e.g., in cases of extraocular myositis with subsequent fibrosis, with agenesis of the extraocular muscle(s) or extraocular muscle avulsion in cases of trauma) (Allgoewer *et al*., 2000).

Neuromuscular strabismus due to a dysfunction of CN III, IV or VI can be caused by orbital or intracranial disorders including congenital, inflammatory, idiopathic, infectious, neoplastic and traumatic processes. With intracranial disorders, neuromuscular strabismus might be seen as a part of the middle cranial fossa syndrome (see below). Dysinnervation of the extraocular muscles has been reported in dogs as a cause of congenital strabismus (Mari *et al*., 2017). However, in most of the cats and dogs with congenital neuromuscular strabismus, an identifiable underlying cause is not found.

Congenital divergent strabismus (exotropia), which may be unilateral or bilateral, occurs in brachycephalic breeds, including the Boston Terrier, English Bulldog and Pekingese. Vision and eye movements are normal and the

condition appears non-progressive. Although no cause has been identified, paresis and abnormal caudal insertion of the medial rectus muscle have been suggested as possible explanations.

Congenital convergent strabismus (esotropia) has been reported in albino and imperfect albino cats (including, Bengal, Birman, Himalayan and Siamese cats). This type of convergent strabismus is not present at birth but develops during the first 6 months of life (Blake *et al*., 1974). The majority of the axonal projections from the temporal retina usually do not cross at the level of the optic chiasm, but in these cats, there is increased crossover. During development there is disorganization of the retina, aberrant crossing of optic nerve axons at the optic chiasm, alterations in speed of axonal migration and misrouting of axonal processes within the rostral colliculus, lateral geniculate nucleus and visual cortex. Affected animals are able to make some sense of the conflicting visual inputs by blocking the projections of the inappropriately crossed afferents into the visual cortex and thus restore some vision. However, the consequence is that the consciously perceived visual field and binocularity are reduced. The convergent strabismus may be the result of a compensatory attempt to obtain increased overlap of the left and right visual fields. The degree of eye misalignment varies greatly among affected cats, with some exhibiting grossly deviated eyes while others have only a hint of strabismus. This might be due to the irregular proportion of crossing axons at the level of the optic chiasm not constant in these cats, and neither is the pattern of anomalous visual projections to the visual cortex and rostral colliculus (Blake *et al*., 1974)

Retrobulbar swelling or mass may interfere with normal eyeball movement; affected cases usually present with exophthalmos, protrusion of the third eyelid and occasionally restriction of the function of the extraocular muscles, leading to a mechanical strabismus.

Animals with obstructive (congenital) hydrocephalus might present with strabismus (usually ventrolateral and bilateral). The strabismus may be due to orbital skull malformations, rather than to neuromuscular dysfunction and has been referred to as the ‘setting sun sign’. Increased intracranial pressure in hydrocephalus was reported to affect oculomotor nerves in children, leading to lateral strabismus, and this could potentially be considered in veterinary medicine as a possible underlying cause for this clinical presentation (Altintas *et al*., 2005).

Involvement of the cranial nerves that innervate the extraocular muscles in animals with tetanus might lead to restrictive divergent strabismus.

**Abnormal eye movement**

There are four basic types of eye movements: saccade (rapid movement of the eye in the same direction to an intended new position for the fixation of visual stimulus); smooth pursuit (continuous tracking of slowly moving visual objects); vergence (disconjugate movement of the eyes to allow fusion and binocular vision); and vestibulo-ocular movements (to keep the eyes stable during head rotations, maintaining image stability). The most common abnormal eye movement described in veterinary medicine involves pathological nystagmus and involuntary saccadic eye movement.

It is also important to recognize cases with iridodonesis, a condition in which the iris vibrates during eye movements. This occurs when there is lens subluxation or with the absence of a lens (aphakia) and should not be confused with other abnormal eye movements.

**Pathological nystagmus**

Physiological jerk nystagmus is a rhythmical and reflexive eyeball movement, which can be assessed clinically by performing the vestibulo-ocular reflex (VOR). Pathological jerk nystagmus occurs with unilateral dysfunction of the

vestibular system. Physiological jerk nystagmus and pathological jerk nystagmus are absent with bilateral symmetrical vestibular dysfunction. The abnormal jerk nystagmus may be continuous (resting or spontaneous nystagmus) or may be observed when the head changes position (positional nystagmus). The direction of nystagmus is defined as the direction of the fast phase of the nystagmus (right or left), and as the plane of rotation (horizontal, vertical, or rotatory). The fast phase direction is usually away from the side of the lesion, except in cases of central vestibular disease with a paradoxical vestibular dysfunction. Pathological vertical nystagmus has been associated with dysfunction of the central vestibular system; however, this clinical sign should not be the only sign used to differentiate between a central and peripheral vestibular dysfunction.

**Congenital pendular resting nystagmus**

Congenital pendular resting nystagmus (where eye movements are equal in velocity in both directions) may occur secondary to congenital abnormalities of the visual pathway. Congenital pendular resting nystagmus has been reported in Belgian Shepherd Dogs where the decussation of the axons is lost at the level of the optic chiasm and all the retinal projections are into the ipsilateral optic tract (Hogan and Williams, 1995). However, in albino and imperfect albino cats (including Birman, Himalayan and Siamese cats), which also suffer from congenital pendular nystagmus, this disorder might be due to an excessive contralateral decussation of the axons at the level of the optic chiasm. Therefore, animals affected with congenital pendular resting nystagmus might have some aberration of the architecture of the visual pathway as the common factor.

**Amaurotic, wandering or searching nystagmus**

This may be recognized in association with ocular abnormalities and congenital visual deficits, particularly if complete blindness is present from birth. The nystagmus associated with congenital visual deficits is characterized as either a continuous fine oscillation of both globes (often rotary) or random eye movements (amaurotic nystagmus or 'searching nystagmus'). Searching/amaurotic nystagmus has been described in association with microphthalmos and congenital cataracts in puppies. Animals that lose their vision at a young age may also develop amaurotic nystagmus (Ferreira and Peterson-Jones, 2002) A recent case report described a monocular nystagmus representing the Heimann-Bielschowsky phenomenon (as it is known in human literature) due to a unilateral congenital cataract with visual impairment (Liatis and Cherubini, 2020). The term 'nystagmus' in amaurotic/searching nystagmus might be wrongly used, as these abnormal eye movements might represent vergence eye movement abnormalities rather than a dysfunction of the vestibulo-ocular system.

**Involuntary saccadic eye movement**

Involuntary saccadic eye movements are characterized by spontaneous, rapid, usually non-rhythmic, unsustained saccadic oscillations without the slow drift seen in pathological jerk nystagmus. Involuntary saccadic eye movements should be distinguished from pathological jerk nystagmus as they represent different neurolocalizations. Saccadic oscillations are divided into two broad categories: those with an intersaccadic interval between subsequent saccades (macrosaccadic oscillations); and those lacking such an interval (opsoclonus). Opsoclonus and macrosaccadic oscillations have been reported in dogs and cats (Ives *et al*., 2018) with diseases affecting the cerebellar function, including corticosteroid-responsive tremor syndrome and neuronal ceroid lipofuscinosis).

Another type of saccadic oscillation described in veterinary medicine is the convergence-retraction nystagmus, which ideally should be referred as convergence-retraction oscillations as it represents a disorder of the saccades rather than dysfunction of the vestibulo-ocular system. Convergence-retraction oscillations are irregular eye

movements in which both eyeballs rhythmically converge and retract into the orbit, particularly on attempting an upward gaze. The affected animals also show an inability to move the eyes dorsally when attempting an upward gaze. Convergence-retraction oscillations appear to be a highly specific neurological sign localizing to the dorsal midbrain (tectum and dorsal aspect of the tegmentum), which, in combination with patient signalment and history, may be more suggestive of certain aetiologies including vascular, inflammatory or neoplastic diseases (Canal *et al*., 2015; Crawford *et al*., 2019; Liatis *et al*., 2020). In humans, this type of abnormal eye movement is seen as part of Parinaud's syndrome, also known as dorsal midbrain syndrome (Ortiz *et al*., 2021).

**Pupil abnormalities**

The function of the pupil and its size is controlled by the interaction of the parasympathetic and the sympathetic nervous system (previously explained). The parasympathetic nervous system controls the light reaction, with its major centre in the rostral midbrain (pretectal and oculomotor nuclei). The sympathetic nervous system controls the dilator muscle of the iris directly or indirectly (by inhibiting the oculomotor nucleus in the midbrain). The normal function of the pupils involves being isocoric (ideally in a dark room) and reacting bilaterally to light stimulus.

Pupillary disorders may involve the visual system or the autonomic system. Disorders of pupils due to dysfunction of the parasympathetic nervous system will affect the pupillary light reflex. Disorders of the iris muscle (iris atrophy, application of cholinergic agents) also need to be considered in impaired pupillary light reflex. The lack of sympathetic innervation to the eye is clinically known as the Horner syndrome. The clinical sign of pupil abnormalities might present as anisocoria (asymmetrical pupils), bilateral miosis (both pupils constricted), bilateral mydriasis (both pupils dilated), dyscoria (abnormality in shape or form of the pupil mainly seen in cats as a hemidilated pupil) and pupillary hippus (pupillary athetosis).

**Anisocoria**

Anisocoria is a condition characterized by unequal pupil size. The underlying cause may be physiological, pathological or pharmacological in origin. The prevalence of physiological anisocoria is not well reported in veterinary medicine but up to 14% of normal people have different sized pupils (George *et al*., 2019). Pathological anisocoria indicates a lesion causing dysfunction of the sympathetic or parasympathetic innervation of the iris muscle or a dysfunction of the iris muscle itself (such as iris atrophy). Pharmacological anisocoria is caused by a pharmacological agent. Mydriatic agents (to dilate the pupil) include sympathomimetic, parasympatholytic medications and psychoactive drugs such as cocaine and amphetamine. Miotic agents (to constrict the pupil) include parasympathomimetic drugs such as pilocarpine (Stanely, 2008).

The resting pupil size and possible asymmetry should be assessed using a direct ophthalmoscope from a distance in normal light and then in a darkened room. The neurological causes of anisocoria with normal vision involve lack of parasympathetic tone to the iris constrictor muscles (mydriatic pupil) or lack of sympathetic tone to the iris dilator muscles (miotic pupil, Horner syndrome).

The initial assessment of anisocoria starts by excluding dysfunction of the iris muscle (such as atrophy, posterior synechia, surgical injury after cataract surgery) or the possibility of a pharmacological anisocoria. When this has been excluded, the clinician should first determine which pupil is abnormal. Observation of pupil size in dim and light environments using retroillumination by the direct ophthalmoscope can help to recognize the abnormal pupil

**Mydriasis**

The parasympathetic component of the oculomotor nerve, the ciliary ganglion and the short ciliary nerves, can be affected by a lesion located between the rostral midbrain (nucleus of the parasympathetic component of the

oculomotor nerve) and the periorbita and cause a dilated and unresponsive pupil with normal vision (normal menace response, absent direct PLR when the affected pupil is tested and absent indirect PLR when the contralateral eye is tested). In some cases, a mydriatic pupil with normal vision (internal ophthalmoplegia) could be the first indication of middle cranial fossa syndrome (discussed later) and also present in conjunction with a lateral neuromuscular strabismus due to involvement of the motor component of the oculomotor nerve.
Documented cases of feline and canine internal ophthalmoparesis/ophthalmoplegia are limited in the veterinary literature.

In dogs, this condition has been reported in the literature secondary to intracranial neoplasia, contact toxicity (e.g. to *Datura stramonium*), or as an idiopathic cause (discussed later) (Lewis *et al*., 1984; Larocca, 2000; Hansen *et al*., 2002; Tetas *et al*., 2017).

Feline internal ophthalmoparesis/ophthalmoplegia often presents with other clinical signs based upon a report of a referral hospital population (Hamzianpour *et al*., 2018). A thorough history, physical examination, neurological and ophthalmic examinations are essential for clinical reasoning and to select the most appropriate diagnostic tests effectively. Cats with intracranial lesions can present with internal ophthalmoparesis/ophthalmoplegia as the sole neurological clinical sign. Advanced imaging might be necessary to reach a definitive diagnosis, but abdominal ultrasound can be helpful in some cases with systemic disease such as lymphoma. Cats with systemic and neurological deficits related to internal ophthalmoparesis/ophthalmoplegia have a guarded prognosis due to the high prevalence of neoplasia (such as lymphoma and pituitary neoplasia) in this population (Hamzianpour *et al.,* 2018).

Anisocoria and size difference of palpebral fissures, caused by certain lesions affecting the deep cerebellar nuclei, has been reported in experimental studies and suspected in some clinical reports (Holliday, 1979; Cherubini *et al.,* 2007). Experimental studies have shown that ablation of the fastigial nucleus might cause contralateral mydriasis, while unilateral ablation of the interposital nucleus might lead to ipsilateral mydriasis and an ipsilateral widened palpebral fissure (Holliday, 1979).

**Canine idiopathic oculomotor neuropathy**

Canine idiopathic oculomotor neuropathy has been described in the veterinary literature (Tetas *et al.,* 2017). This should be considered as a differential diagnosis for dogs presenting with unilateral oculomotor neuropathy (with parasympathetic and/or motor dysfunction) with the absence of other neurological and ophthalmic signs and with advanced imaging lesions restricted to CN III . These cases can have a good prognosis, as the clinical signs do not deteriorate or can even improve without treatment (Tetas *et al.,* 2017).

**Hemidilated pupil**

A hemidilated (D-shaped) pupil is the consequence of vulnerability to paralysis of the ciliary nerves supplying the iris constrictor muscles in cats. It is particularly seen with feline leukaemia virus- (FeLV-) associated lymphoma infiltration (Collins and O'Brien, 1990; Roberts, 1992). Either of the two ciliary nerves, the lateral (malar) ciliary nerve or medial (nasal) short ciliary nerve, may be affected and, depending on which nerve is affected, this results in either a D-shaped or a reverse D-shaped pupil. Hemidilated pupils have also been described with apparent lymphoma invasion of the medial iris stroma in both eyes of a cat (Nell and Suchy, 1998).

**Horner syndrome**

Lesions affecting the sympathetic innervation to the head result in Horner syndrome and loss of cutaneous vascular tone on the affected side, with peripheral vasodilatation. Horner syndrome bears the name of Johann Friedrich Horner (1831--1886), a Swiss ophthalmologist who published a case report in 1869. The French ophthalmologist Claude Bernard was the first to identify the triad of findings as the dysfunction of the sympathetic innervation to the eye in 1852. Therefore, this condition is sometimes called Claude Bernard--Horner syndrome, especially in the French literature. The loss of cutaneous vascular tone in some dogs and cats is evident as increased cutaneous temperature (the pinna on the affected side being warmer than the unaffected side) and hyperaemia. The effects of loss of cutaneous vascular tone on the eye include mild congestion of the scleral blood vessels and a decrease in intraocular pressure. Horner syndrome describes the specific ophthalmic changes associated with loss of sympathetic innervation:

- Miosis (constriction of the affected pupil) -- Avulsion of the brachial plexus nerve roots usually cause only a partial Horner syndrome, often with miosis as the only feature. This is typically because only the T1 nerve root of the T1--T3 sympathetic outflow is affected by brachial plexus avulsions. Partial Horner syndrome (with miosis as the only feature) may also occur with acute and severe lateralized cervical spinal cord disease, but the expectation would still be for the majority of cases to have complete Horner syndrome (Griffiths, 1970)
- Enophthalmos -- Loss of sympathetic innervation leads to the loss of orbital smooth muscle tone and sinking of the globe into the orbit
- Protrusion of the third eyelid (nictitating membrane) -- Whilst in the dog this occurs passively secondary to enophthalmos, in the cat, the protrusion is due to a combination of enophthalmos and loss of third eyelid retraction
- Ptosis (drooping) of the upper eyelid and decreased tone of the lower eyelid -- This occurs as a result of loss of smooth muscle tone affecting the Müller's muscle
- Conjunctival hyperaemia due to the loss of cutaneous vascular tone.

The miotic pupil in patients with Horner syndrome is most noticeable in the dark because the normal pupil dilates and the affected pupil remains miotic. Horner syndrome results from lesions affecting the first, second (preganglionic) or third order (postganglionic) neurons and it is classified as first order, second order or third order Horner syndrome respectively. The presence of other clinical signs in association with Horner syndrome can help to localize the lesion and, using clinical reasoning, the clinician can formulate the differential diagnosis list.

Pharmacological testing should only be treated as a guide and it should not be used as the sole diagnostic test to localize the lesion (Lockhart *et al.,* 2021). Confirmation of Horner syndrome in cases where this is not immediately apparent can be achieved using topical cocaine; however, this is only rarely required, as failure of the affected pupil to dilate in the dark and other features of Horner syndrome are usually conclusive. Topical administration of 4% or 10% cocaine eye drops results in dilation of the pupil in normal patients, but no pupil dilation is seen with sympathetic dysfunction. Cocaine blocks noradrenaline (norepinephrine) reuptake, resulting in prolonged activity of noradrenaline in the synaptic cleft and consequently pupil dilation. However, in Horner syndrome there is a lack of noradrenaline in the synaptic cleft and therefore the pupil fails to dilate. Pupil size should be determined prior to the administration of cocaine eye drops and again after 30--60 minutes.

In cases where Horner syndrome has been present for some time (usually at least 7--14 days), denervation hypersensitivity resulting from sympathetic denervation enables pharmacological testing to be performed to predict the site of the lesion based on increased sensitivity to topical phenylephrine. The time to pupillary dilatation following

topical administration of 1% phenylephrine to both eyes should be determined. Essentially, the shorter the time to pupillary dilatation, the closer the lesion is to the iris:

- Less than 20 minutes suggests third order Horner syndrome
- 20--45 minutes suggests second order Horner syndrome
- 60--90 minutes suggests first order Horner syndrome or no sympathetic denervation of the eye
- If 10% phenylephrine is used, mydriasis occurs in 5--8 minutes with postganglionic (third order neuron) lesions.

A recent study suggested that advanced imaging of the entire sympathetic innervation to the eye should be offered, where possible, in all cases of canine Horner syndrome (Lockhart *et al.,* 2021). The study revealed that where Horner syndrome is seen in dogs as the sole clinical sign, this is very likely to be idiopathic; Golden Retrievers were shown to be significantly over-represented.

The prognosis depends to a large degree on the underlying neurological disease, but is excellent in idiopathic Horner syndrome (which is largely cosmetic and, in many cases, may resolve spontaneously). Treatment is rarely required but in cases with bilateral Horner syndrome and where vision is obscured by third eyelid protrusion, topical 1% or 10% phenylephrine can be used to provide occasional short-term alleviation of the clinical signs. Maximal effect occurs for up to 2 hours and in some cases the effect may be maintained for up to 18 hours.

**Pourfour du Petit syndrome**

Mild pathological insult to the sympathetic supply to the head (most likely adjacent to the middle ear) may lead to irritation of the sympathetic fibres, resulting in sympathetic hyperactivity rather than sympathetic denervation. Pourfour du Petit syndrome (excessive sympathetic tone to the eye; the opposite of Horner syndrome) was first described in human patients and has subsequently been reported as a rare finding in cats (Boydell, 2000). The excessive sympathetic tone to the eye results in pupil dilatation, an enlarged palpebral fissure and subtle exophthalmos of the affected side. The prognosis is good for a full recovery, depending on the nature of the underlying cause.

**Pupillary hippus**

Pupillary hippus, also known as pupillary athetosis, involves brief oscillations of pupillary size and may occur as a normal feature in response to light exposure. Very exaggerated hippus may be an indication of CNS disease, particularly if it occurs in conjunction with other neuro-ophthalmological abnormalities.

**Dysautonomia**

Bilateral pupillary dilatation that is not responsive to light, protrusion of the third eyelids and decreased tear production, in the presence of normal vision, are features of canine and feline dysautonomia (also called Key--Gaskell syndrome in cats) (Wise and Lappin, 1990; Longshire *et al*., 1996). The ocular changes are also associated with profound systemic signs of autonomic dysfunction, in particular lethargy, anorexia, decreased saliva production, megaoesophagus, bradycardia and occasionally faecal and urinary incontinence. The canine and feline syndromes are both rare and occur sporadically. The treatment is purely supportive and the prognosis is guarded. Pharmacological testing may be useful to confirm sympathetic and parasympathetic dysfunction.

**Pharmacological evaluation of pupil function**

There are pharmacological testing procedures that can be used to determine if the dysfunction is preganglionic or postganglionic in both parasympathetic and sympathetic denervation. These tests rely on denervation hypersensitivity, and postganglionic lesions will respond quicker. Denervation hypersensitivity takes about 7 days to occur after the onset of clinical signs, which limits the use of these tests. Moreover, the tests should ideally not be used as the only method to localize the lesion as they are considered not reliable by some authors. Pharmacological testing of pupil function may be useful in two situations:

- To confirm the neurological nature of a lesion, i.e. whether it is a sympathetic dysfunction (Horner syndrome) or a parasympathetic dysfunction. However, in most cases the nature of the lesion can be ascertained based on the characteristic appearance and response of the pupils to light stimuli and the dark, and pharmacological testing is not required. Examination of pupil function must always be performed prior to pharmacological testing
- To ascertain the site of lesions affecting the efferent arm of the PLR and the sympathetic supply to the eye (Horner syndrome). However, pharmacological testing is not an exact science and the time to a response should be used only as a guide to the site of the lesion. There are differences in opinion on the utility of this form of testing and on the concentration of drugs used.

The basis of the tests lies in the development of denervation hypersensitivity (Rosenblueth and Cannon, 1936). There are a number of considerations when performing pharmacological testing:

- Testing should always be performed in both eyes, using the normal eye as a comparison
- The pharmacological agent should be instilled into the conjunctival sac at an equal volume and concentration in both eyes. A second dose should be instilled after a few minutes in case the first dose was washed away by induced tear production
- Contact with or manipulation of the eye should be avoided during pharmacological testing as this can affect drug absorption or induce tear production, which may dilute the pharmacological agent
- The light intensity and degree of stimulus should remain constant throughout the test.

Pharmacological testing of the sympathetic nervous system is discussed in more detail under Horner syndrome. Lesions affecting the efferent arm of the PLR (parasympathetic lesions producing mydriasis) can be localized further by application of direct and indirect parasympathomimetics.

- The use of a direct parasympathomimetic (0.1% pilocarpine drops) may allow confirmation of a parasympathetic lesion and differentiation between pre- and postganglionic lesions. Iris constriction occurs rapidly in the affected eye with postganglionic lesions due to denervation hypersensitivity but has little effect on the normal eye (Antonio-Santos, 2005). The test depends on achieving a specific concentration of pilocarpine at the iris and therefore a formulation that includes a vehicle to enhance corneal penetration (e.g. benzalkonium chloride) should be used (Carter, 1979). In human patients false-positive responses are more common with pilocarpine concentrations >0.2%, and false-negative responses may occur at concentrations <0.05% (Younge and Bruski, 1976). In practice this test is often non-specific, with a response indicating only that the lesion is neurological, rather than specifying the site. For example, this test can be used to differentiate mydriasis due to iris disease or pharmacological blockade from atropine or atropine-like substances (both of which are unresponsive to pilocarpine) from neurological disease (Scagliotti, 2000).

Topical pilocarpine can be irritant to the eye and may induce a blepharospasm that can last up to 12 hours; owners should be warned of this prior to performing the test.

- Differentiation between pre- and postganglionic lesions (ciliary ganglion) can be achieved by the topical administration of an indirect parasympathomimetic (0.5% physostigmine drops). Physostigmine inhibits cholinesterase, thereby increasing the concentration of acetylcholine at the neuromuscular junction. If the postganglionic neuron is preserved, it apparently releases low levels of acetylcholine continuously, the local concentration of which is increased by application of physostigmine. With preganglionic lesions, iris constriction occurs before the control eye due to denervation hypersensitivity. However, with postganglionic lesions, physostigmine has no effect. Physostigmine causes peak pupil constriction at 30 minutes in human patients, with a return to normal at around 90 minutes. If neither pupil responds, the test is considered a false-negative and must be repeated.

**Third eyelid protrusion**

Protrusion of the third eyelid may occur passively following loss of sympathetic tone to the orbit (Horner syndrome, dysautonomia and systemic illness), in conditions causing enophthalmos and secondary to retrobulbar masses. Intermittent, brief protrusion of the third eyelid may occur in tetanus (Timoney *et al*., 1988).

Haw's syndrome is bilateral protrusion of the third eyelid of unknown cause and occurs in young cats in the absence of other systemic and ophthalmic abnormalities. It has been suggested to occur in dogs, in particular the Golden Retriever (Gelatt, 2000). The condition may develop following a history of diarrhoea and generally persists for some time before gradually resolving. Confirmation of the diagnosis is possible by demonstrating that topical administration of 1--2% adrenaline or 10% phenylephrine can temporarily abolish the third eyelid protrusion (by stimulating smooth muscle contraction). The disorder can be easily differentiated from bilateral Horner syndrome by the absence of concurrent miosis and from dysautonomia by demonstrating normal pupil dilatation in the dark and constriction in the light.

**Neurogenic keratoconjunctivitis sicca**

Keratoconjunctivitis sicca is considered neurogenic (NKCS) when the lesion affects any part of the parasympathetic innervation to the lacrimal gland by the facial nerve (CN VII) (previously described). Depending on the location of the lesion along this parasympathetic pathway, other neurological deficits may be present.

NKCS may be present with ipsilateral xeromycteria (dry nares) if the lesion affects the preganglionic parasympathetic fibres or if the lesion is located at the level of the pterygopalatine ganglion. Ipsilateral facial paralysis and ipsilateral xeromycteria may be present in conjunction with neurogenic KCS if the lesion occurs proximal or at the level of the geniculate ganglion. If the lesion occurs at the level of the internal acoustic meatus, then peripheral vestibular signs may also be present in conjunction with facial paralysis, NKCS and xeromycteria. If the lesion is at the level of the medulla oblongata, other brainstem signs in conjunction with the facial paralysis, NKCS and xeromycteria will be present (altered mental status, ipsilateral postural reactions deficits, facial paralysis, and the possibility of other cranial nerves affected).

The most common underlying causes of NKCS in dogs have been reported as idiopathic facial paresis (53%), followed by occurring secondary to an endocrinopathy (18%), otitis interna (12%), head trauma (9%), iatrogenic (3%), brainstem mass (3%), and an area of inflammation in the pterygopalatine fossa (3%) based upon a recent retrospective study (Galley *et al.,* 2021). The majority of dogs in that study received treatment with oral pilocarpine,

topical ciclosporin, or a combination of the two. Treatment with oral pilocarpine (with or without topical ciclosporin) was linked to a better outcome (Galley *et al.,* 2021).

**Increased tear production**

Paradoxical tearing (gusto-lacrimal reflex or 'crocodile tears') describes the syndrome of excessive tear production whilst eating or during anticipation of a meal. The syndrome has been recognized for a considerable time in humans (Lutman, 1947) and has subsequently been described in the cat (Hacker, 1990). The underlying cause in humans is thought to be aberrant regeneration of facial nerve fibres following trauma, with fibres that usually innervate the salivary glands being misrouted to the lacrimal gland. The name 'crocodile tears' was derived from the popular myth that crocodiles cry whilst eating their prey.

**Neurotrophic keratitis**

Neurotrophic keratitis is a type of neurogenic keratitis and poor corneal healing due to loss of corneal sensation, which is provided by the ophthalmic branch of the trigeminal nerve (previously discussed). Lesions of the ophthalmic branch of the trigeminal nerve result in loss of sensation to the cornea and medial canthus of the eye (as well as the inner surface of the nostrils and nasal cavity). The consequence of this is loss of the corneal and palpebral reflexes. The menace response should still be intact if vision and the facial nerve are not involved. Neurotrophic keratitis to ulcerative keratitis, is a frequent complication of ophthalmic branch lesions but is infrequently seen following facial nerve (motor) lesions (except in dog breeds with marked exophthalmos, e.g. Pugs). Although basal tear secretion should be normal, reflex tear production in response to stimulation of the cornea or nasal mucosa is lost as this is mediated via the ophthalmic branch of the trigeminal nerve. Blinking to spread the tear film is also reduced as the perception of corneal drying is reduced or lost. If the mandibular branch of the trigeminal nerve is affected, the resulting masticatory muscle atrophy causes an increase in the retrobulbar space and consequently a pronounced enophthalmos

**Facial nerve paresis/paralysis**

One of the functions of the facial nerve is innervation of the orbicularis oculi muscle, which is responsible for closing the eyelids. Decreased or absent function of the orbicularis oculi muscle results in a decrease in, or loss of, the menace response and palpebral reflex. The normal retraction of the globe during the corneal reflex is maintained if the trigeminal nerve is preserved. Blinking is responsible for spreading the tear film over the cornea; therefore, loss of blinking may predispose to exposure keratitis (although this is more common when there is concurrent reduced tear production or trigeminal nerve damage).

**Middle cranial fossa syndrome**

Middle cranial fossa syndrome (also known as cavernous sinus syndrome) is a clinical disorder characterized by dysfunction of several cranial nerves that course at the level of the middle cranial fossa and pass through the orbital fissure, which includes CN III (motor and parasympathetic component); CN IV; CN VI; ophthalmic branch of the CN V; and postganglionic sympathetic nerve fibres. The maxillary branch of the CN V, which passes through the round foramen, can also be affected.

The most common clinical signs involve internal and external ophthalmoparesis/plegia. Internal ophthalmoplegia refers to paralysis of the iris and ciliary muscles (mydriasis), whereas external ophthalmoplegia refers to paralysis of the extraocular muscles (ipsilateral absent VOR). The term pan-ophthalmoplegia can also be used if there is external and internal ophthalmoplegia. When the iris, ciliary or extraocular muscles are incompletely

paralyzed (some movements are still present), the term ophthalmoparesis is applied. Fixed mid-range pupils can also be present if there is involvement of both the parasympathetic and the sympathetic innervation of the iris. Ipsilateral sensory deficits of the ophthalmic (reduced to absent corneal sensation, reduced to absent corneal reflex and nasofacial hypoalgesia) and maxillary (periorbital hypoalgesia) branches of CN V can also be present in middle cranial fossa syndrome.

Middle cranial fossa syndrome is an anatomical diagnosis, the most common reported aetiologies are neoplasia or infectious disorders (Theisen *et al.*, 1996; Jones *et al.*, 2018; Osinchuk *et al.,* 2019). The treatment is based on the underlying cause. Immunosuppressive medications could be considered in cases on inflammatory disorders of unknown origin (suspected immune-mediated), while radiotherapy has been proven to be beneficial in cats and dogs with pituitary masses and in humans with middle cranial fossa syndrome caused by neoplasia (Jones *et al.*, 2018). Surgical approaches are limited to normal sized or moderately enlarged pituitary masses. The mean survival time for dogs with middle cranial fossa syndrome has been reported as 135 days; however, all the dogs in that study presented with extensive tumours. The overall prognosis associated with middle cranial fossa syndrome in dogs and cats is considered guarded to poor; however, the published cases are limited to severe infectious disease or extensive neoplasia.