Joel’s Rules/Advice:
1. Neurologist always start with: levelize, lateralize, localize
2. In medical school (and beyond) you really do need to know:
   a. the three cranial nerves that move the eyeball, the muscles they supply, and what each muscle does
   b. the extra functions of cranial nerve 3
   c. the medial longitudinal fasciculus (MLF) syndrome (aka internuclear ophthalmoplegia, [INO]) gets asked about a lot.
3. Lesions above the brainstem produce abnormal eye movements that remain conjugate.
4. If the two eyes do not stay conjugate, if there is a brain lesion it is at or between cranial nerves 3, 4, 6.
5. Lesions of cranial nerve 3, 4, 6 weaken muscles (i.e. no matter how you test it, the muscle is always weak; this is a lower motor neuron [LMN] injury).
6. Lesions between cranial nerves 3, 4, 6 impair movements (i.e. depending on how you test it, the movement may or may not fail; if supranuclear, this is an upper motor neuron [UMN] injury).
7. To determine weakness, make the muscle do what it is supposed to do (sounds simple, somehow easily forgotten)
8. Not everything is known, and not everything makes sense (to us).

Highlights you should know (at least some day) from reading, study, or class discussion:
1. Some eye movements
   a. The eye is a globe that (like the earth) can rotate around an axis. The eyeball has three kinds of movements, each created by twisting around one of three axes:
      i. **Horizontal movements** are created by a pole that pokes through the eye from top to bottom
         1. abduction: the eyeball rotates to point the pupil outward
         2. adduction: the eyeball rotates to point the pupil inward
      ii. **Vertical movements** are created by a pole that pokes through the eye from left to right
         1. elevation: the eyeball rotates to point the pupil upward
         2. depression: the eyeball rotates to point the pupil downward
      iii. **Torsion movements** are created by a pole that pokes through the eye from front to back
         1. intorsion: the eyeball rotates so that that the top of the orbit rotates toward the nose (the bottom of the eyeball rotates away from it)
         2. extorsion: the eyeball rotates so that that the top of the orbit tilts away from the nose (the bottom of the eyeball rotates toward it)
2. Eye movement control depends on coordination at several levels of the nervous system.
   a. Peripherally, there are 6 muscles that move the eyeball

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Main action</th>
<th>Lesser action(s)</th>
<th>CN</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral rectus</td>
<td>Abduction</td>
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<td>6</td>
<td>Only thing CN6 does</td>
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<td>(LR)</td>
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<td>Superior rectus</td>
<td>Elevation</td>
<td>Adduction</td>
<td>3</td>
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<td>(SR)</td>
<td>(when eye is abducted)</td>
<td>Intorsion</td>
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<tr>
<td>Inferior rectus</td>
<td>Depression</td>
<td>Adduction</td>
<td>3</td>
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<td>(IR)</td>
<td>(when eye is abducted)</td>
<td>Extorsion</td>
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<td>Superior oblique</td>
<td>Depression</td>
<td>Adduction</td>
<td>4</td>
<td>Only thing CN4 does; Oblique = weird</td>
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<tr>
<td>(SO)</td>
<td>(when eye is adducted)</td>
<td>Intorsion</td>
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<tr>
<td>Inferior oblique</td>
<td>Depression</td>
<td>Adduction</td>
<td>3</td>
<td>Oblique = weird</td>
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<td>(IO)</td>
<td>(when eye is adducted)</td>
<td>Intorsion</td>
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<tr>
<td>Medial rectus</td>
<td>Adduction</td>
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<td>(MR)</td>
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b. Centrally, the main role players are
   i. frontal, parietal, and occipital cortex
      1. EG: area 8 (“frontal eye field”) in posterior frontal lobe drives both eyes horizontally to gaze in the contralateral direction
   ii. cranial nerves 3, 4, and 6 nuclei and nerve
   iii. fiber pathways between these
      1. supranuclear cortical fibers descending to innervate the nuclei
      2. medial longitudinal fasciculus (MLF) allows CN 6 to coordinate with the contralateral CN3
3. There are different types of eye movements to control
   a. Saccades: voluntarily move eyes from one point, quickly to another
   b. Smooth pursuit: Follow a moving object
   c. Vergence: Point both eyes inward to look at something near
   d. Vestibulo-ocular movements: Reflexive movements to adjust for head movement
   e. Fixation: Keep eyes on a stationary target.

4. Eye movement findings (clinically)
   a. dysconjugate movements: One eye is looking at a different place than the other
   b. nystagmus: rapid, rhythmic jerking of eyeball
   c. neighborhood findings
      i. ptosis: droop of upper eyelid
      ii. anisocoria: unequal pupil diameters
      iii. midriasis: pupil is too big
      iv. miosis: pupil is too small

Below are some cases written by Dr. Thomas P. Bleck. Use these for practice, and to be able to apply material learned in your reading and in class. From a clinician’s point of view, these cases are all fairly classic and would not be unusual for you to see in the real life of patient care.

Case I
A 43 year old man is found sprawled on the ground in a public park. He is breathing 12 times per minute and has a pulse of 110 beats per minute. He does not speak or follow commands to move his face, arms, or legs. He wears a medic alert bracelet indicating a history of hypertension and diabetes mellitus. His eyes are closed, but when they are held open he is noted to have spontaneous conjugate horizontal movements of the eyes from side to side.

Questions:
1. What anatomic systems are responsible for horizontal conjugate gaze in unconscious patients?

In horizontal gaze, the eyes must move in close synchrony. The problem is that horizontal eye movements must coordinate a cranial nerve III muscle (medial rectus) with a cranial nerve VI one (lateral rectus). So, there must be a way to keep the IIIrd and IVth nuclei integrated, even though they are in very different areas of the upper brainstem. This system starts in the parapontine reticular formation (PPRF), a collection of neurons near the abducens (VI) nucleus (some consider it a part of that nucleus). The PPRF receives inputs mainly from the contralateral frontal eye field (FEF), located in the posterior lateral frontal cortex. PPRF neurons direct the ipsilateral abducens nucleus (VI) to contract the lateral rectus muscle. This abducts the eye ipsilateral to the PPRF. At the same time, axons that cross over to ascend rostrally in the contralateral medial longitudinal fasciculus (MFL) direct the oculomotor nucleus (III) contralateral to the PPRF to contract the medial rectus muscle. This adducts the eye contralateral to the PPRF. Thus, the left PPRF moves both eyes left, and the right PPRF moves both eyes right.

2. What does the presence of the spontaneous eye movements tell you about the cause of this patient’s unresponsive state?
Impaired level of consciousness requires brain dysfunction somewhere, and there are only a few places where that can be: the reticular activating system, which courses through the brainstem and may poke up into the thalamus, or the bilateral hemispheric cortex. So, if a patient has impaired level of consciousness, there must be dysfunction in the brainstem, bilateral thalamus, or diffuse bilateral cerebral hemispheric cortex. Since horizontal eye movements in this patient remained conjugate, then cranial nerves III and VI were intact as were the PPRF and MLF. So, a good chunk of the brainstem was healthy. The cause of this patient’s unresponsiveness, then, was dysfunction at the very high brainstem, bilateral thalamus, or bilateral cerebral hemispheric cortex. Most likely, it was cortical dysfunction, given the extra vulnerability cortical neurons have to hypoglycemia.

The rescue squad personnel determine that the patient’s blood glucose is 35 mg/dL, and administer 25 grams of glucose. The patient awakes abruptly, and the spontaneous horizontal eye movements are replaced by normal volitional eye movements.

Questions:
1. What cerebral cortical structures are now in command of brainstem eye movement centers? The FEF’s (see above).

2. What different functions do these cortical eye movement centers subserve? Each FEF directs the contralateral PPRF to make the eyes move horizontally, to look away from the FEF in question.

3. Why did the glucose cause the patient to awaken? The patient had hypoglycemia. Since brain cells are so dependent on glucose from the blood (they do not have glycogen stores of their own), hypoglycemia causes brain cells to work poorly. Some brain cells are more vulnerable to this than others. In general, cortical cells are more vulnerable than those in the brainstem (think about why that’s a good way for the system to work). Giving glucose restored the patient to normo-glycemia and restored normal cerebral function.

The patient is transported to the hospital. While waiting in the emergency department, he is found to be confused. When he attempts to look in either horizontal direction, the abducting eye fails to abduct completely, and he reports diplopia. He is given 100 mg thiamine, and within two hours both his mental status and his eye movements are normal.

Questions:
1. What happened? The patient had eye movement abnormalities and delirium after a glucose bolus, resolving with thiamine. This pattern suggests Wernicke’s encephalopathy. This condition occurs in people who are thiamine depleted, often from poor nutrition (e.g. alcoholics, elderly people with poor appetite). Thiamine is necessary for mitochondrial mediated aerobic metabolism of glucose. Without it, nerve cells resort to anaerobic metabolism of glucose, and this can be toxic to nerve cells. Some cells are more vulnerable to this toxicity than others. Brainstem nuclei that control eye movements are especially affected acutely, and neurons in the midline of the diencephalon can die off chronically (especially the mammillary bodies
and mediodorsal nucleus of the thalamus). So, in general, if someone may have a thiamine deficiency, do not give him/her glucose first, because that would worsen the problem! Give thiamine first, and then glucose is OK. If patients survive Wernicke’s encephalopathy (mortality rate is high), if they had suffered permanent diencephalic damage they may go on to have a permanent memory disorder called Korsakoff’s amnesia. These individuals have anterograde amnesia (i.e. they cannot form new memories well) and, most characteristically, they tend to confabulate (make up) memories to “fill in the gaps.”

2. What else could have gone wrong had he not received thiamine?

See above.

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Case II
A 43 year old man is found sprawled on the ground in a public park. He is breathing 12 times per minute and has a pulse of 110 beats per minute. He does not speak or follow commands to move his face, arms, or legs. He does not move his eyes horizontally, but can open his eyes spontaneously or on command. He can move his eyes vertically but not horizontally. He is able to answer yes/no questions by blinking his eyes. He wears a medic alert bracelet indicating a history of hypertension and diabetes mellitus.

Questions:
1. What anatomic systems are responsible for vertical eye movements?
(Compare this to the explanation of horizontal movements.) Vertical movements are coordinated in the brainstem at the level of the midbrain. The areas of cortex that drive this brainstem center are less clear than in horizontal eye movements, but probably involve both frontal and occipital cortex. Anyway, all the vertical eye movements are controlled by either IIIrd or IVth nerve functions, so there is no need for a longitudinally long fiber system (as there was with the MLF and horizontal movements). Thus, this system is less vulnerable to damage. It can be impaired in certain neurological disorders, though (e.g. progressive supranuclear palsy [PSP]). Upgaze depends more on dorsal midbrain (e.g. in Parinaud’s syndrome, a mass such as a pineal gland tumor compresses this area and impairs upgaze). Downgaze depends more on a midbrain system that is a bit more ventral, but still dorsomedial to the red nucleus (rarely, strokes can selectively lesion it). The basic idea is that these midbrain centers have bilateral outputs to the IIIrd and IVth cranial nerve nuclei so as to coordinate movements, as indicated, of the elevator (i.e. superior rectus, inferior oblique) or depressor (i.e. inferior rectus, superior oblique) muscles.

2. Why is he unable to move his arms or legs? His face?

See answer to next item.

3. This problem is typically caused by obstruction in what artery?

Neurologists always start with localizing the lesion. First, this man’s level of consciousness is not impaired. He is awake and alert, as shown by the fact that he can understand language and make correct yes/no answers. So, he could not have anything more than limited damage to the brainstem, thalamus, or cerebral hemispheric cortex. He can move his eyes vertically so the midbrain is largely intact, cranial nerves III and IV are intact, and...
cortical regions directing this system are intact. Since he cannot move his eyes horizontally, he has a lesion of the upper- to mid-pons, with bilateral involvement of the MLF and/or PPRF. A lesion there would also explain his bilateral face/arm/leg weakness, since it could involve the ventrally located corticospinal tracts bilaterally. Since both sides are involved, the lesion has to involve a midline blood vessel or two separate lateral blood vessels. Whenever possible, we try to explain neurological problems from a single lesion or a single level of the neural axis. To do that here, the most common way to get a lesion like this, and in this location, would be from an arterial obstruction at the distal tip of the basilar artery (i.e. just before the origin of the posterior cerebral arteries).

4. Why is he still breathing?
The clot is in the distal basilar only. The proximal basilar, and the vertebral arteries that feed it, are still intact, thus preserving the medulla and caudal pons.

His blood glucose concentration is normal. He is brought to the emergency department and given intravenous tissue plasminogen activator. Over the next several hours he regains most of the abilities he has lost, but remains unable to look to the left conjugately. However, his right eye will adduct when he attempts to converge.

Questions:
1. What structures are involved in looking to the left? 
(See answer to first question from Case I.) To look left, a signal starts in the right FEF, directing the left PPRF to initiate a movement. The left PPRF directs the left VIth nucleus to contract the left lateral rectus muscle, causing the left eyeball to abduct. At the same time, via connections into the right MLF, the right IIIrd nucleus contracts the right medial rectus muscle, causing the right eye to adduct.

2. Which structure(s) do you think are involved here?
The key here is that his right eye can adduct when he looks at an object close up—during convergence. The fact that this occurs means that the right IIIrd nucleus and nerve and the right medial rectus muscle all work just fine, and are all hooked up just fine. The problem is that this intact system is not being driven during left lateral horizontal gaze. So, the problem is with the PPRF-MLF system. Our thinking after that is a bit less clear, because of the way the information we have is worded. If neither eye looks to the left, then this patient’s pattern implies damage to the left PPRF. If only the right eye cannot look left on horizontal gaze, then this patient’s pattern implies damage to the right MLF.

3. What structures are involved in convergence?
Convergence does not involve the MLF at all, since convergence is achieved by simultaneous contraction of the medial rectus muscle of each eye. So, only the IIIrd cranial nerve nucleus and this one target muscles need be intact on each side. The coordination is done at the level of the dorsal midbrain. (Parinaud’s syndrome, described above, usually also causes loss of convergence.)
Case III
A 27-year-old woman sees her physician because of dizziness and difficulty walking. She was well until 7 years ago, when she had an episode of numbness in her legs, poor handwriting, and a staggering gait, which resolved spontaneously over a 3-week period. She was well for the next 5 years, when she again developed some mild difficulty in walking. Again, she improved on her own over a 2-weeks period and did well subsequently. She now presents with a 3-week history of such severe dizziness that it has caused her to a fall several times. Over these past weeks, her walking has deteriorated steadily, and she must now hold onto furniture in order to get around her home. She also complains of double vision when looking off to her right side.

On her physical exam, during cranial nerve testing, the right optic disk appears paler than the left. Her ocular motility is normal on left gaze. However, when she looks to the right, the right eye develops some motor horizontal nystagmus, and the left eye does not completely adduct. On motor examination, muscle tone is increased in the lower extremities; muscle bulk and power are normal. Right ataxia is greater than left on finger to nose testing as well as on heel to shin testing. The sensory examination shows some loss of vibratory perception and proprioception at the toes. She sways when standing with her feet together, and swaying is made worse when she closes her eyes. Her reflexes are brisk throughout, with bilateral extensor plantar responses. She has a broad base when she walks and occasionally lurches to one side or the other. She is unable to perform a tandem gait.

Questions:
1. What is nystagmus

Nystagmus is a rapid, involuntary, rhythmic jerking of an eyeball. In general, it represents a cortical attempt to “bring back” the eyeball into the “correct” position. It can be horizontal, vertical, or rotary. The most common kind of nystagmus is called “jerk” nystagmus. In this kind, the eyeball moves slowly in one direction, and then rapidly in the other direction. By convention, jerk nystagmus is described by the direction of the fast phase (e.g. jerk nystagmus to the right means the eye moves slowly left and rapidly right). See more in the answer to #2 next.

2. What problems might cause failure of adduction of the left eye?

This is most likely an internuclear ophthalmoplegia (INO), also known as an MLF syndrome. Damage to the one MLF causes the eye on that side to fail to adduct during horizontal gaze to the opposite direction. Classically, the normal eye shows horizontal nystagmus. Since cranial nerve III and the medial rectus muscle themselves are unaffected, the eye can still adduct during convergence. Since the MLF is densely myelinated (think about why that’s a good idea), it is a frequent target in multiple sclerosis, a demyelinating disease of the central nervous system. Since it is in a vulnerable spot to be infarcted by occlusions of tiny lateral penetrator arteries off of the basilar artery, it is also frequently damaged by stroke.

3. Can you localize these problems to one place in the nervous system?
No. The patient’s symptoms and signs imply damage in multiple places in the nervous system—one lesion cannot cause all these things. Starting with symptoms, she had bilateral
leg numbness. That requires bilateral involvement of sensory pathways, but that could be anywhere from peripheral nerves up through sensory cortex of the brain. Poor right hand control and unsteady gait sounds like a right cerebellar lesion. Alternatively, if this was really weakness rather than dyscoordination it could have been due to a lesion to the corticospinal tract subserving the right hemibody (i.e. right cervical cord, or left brain). Dizziness could suggest vestibular dysfunction, which could be due to a peripheral inner ear problem, VIIIth nerve or nucleus dysfunction, or caudal brainstem vestibular nuclei dysfunction. She complains of diplopia when looking right, so either her left medial rectus or right lateral rectus is failing to contract. In this patient, we should already suspect MS (crudely defined as “multiple CNS deficits separated by space and time”), so we might suspect a left INO causing left medial rectus failure on rightward gaze.

Turning to signs (i.e. exam findings), she had a left INO. So, there was damage in the rostral pons involving the left MLF. She also has a pale right optic disk, implying demyelination of the right optic nerve. She has bilateral upper motor neuron (UMN) signs in her legs (increased tone, hyper-reflexia, upgoing toes) implying bilateral corticospinal tract lesions in the thoracic cord (most likely to be there because there were no UMN signs in her arms). Right greater than left hand ataxia confirms the above speculated right cerebellar lesion. Bilateral posterior column involvement is suggested by the wide base while walking (it decreases the need for proprioceptive feedback to keep one standing), poor tandem walking, loss of vibratory and position sense, and positive Romberg sign.