Hi, my name is Toby Yanowitz, I’m going to speak to you today about brain injury in the premature newborn. 50,000 infants are born each year at less than 1500 grams, of these 85% survive, of survivors 5 to 15% will develop what’s called a major disability including cerebral palsy, mental retardation, hearing loss and visual impairment. An additional 25 to 50% will develop a minor disability including borderline intelligence, learning disabilities, inattention and hyperactivity disorders and motor and coordination. Some of these developmental disabilities can be predicted in the neonatal period when we see cranial imaging findings of intraventricular hemorrhage, periventricular leukomalacia and complications of IVH and PVL. The goals of today’s talk is to discuss the origins of intraventricular hemorrhage and periventricular leukomalacia concentrating on a description of the lesions, description of the pathogenesis including both anatomic and physiologic factors and some information about outcomes.

Intraventricular hemorrhage or IVH occurs in 30 to 40% of infants who are born at less than 1500 grams birth weight. The risk of IVH is inversely related to gestational age. The risk of bleeding is greatest in the first 4 to 5 days after birth irrespective of the gestational age. More than 50% of lesions are detected in the first 6 to 12 hours of life and the earlier the onset portends an increased risk for parenchymal involvement. IVH is graded by what we call a Papile grade. Grade I includes the germinal matrix hemorrhage only. In Grade II IVH there is blood in the intraventricular space. In Grade III the intraventricular blood is accompanied by ventricular dilation. And Grade IV IVH refers to parenchymal bleed with or without intraventricular blood.
This is an example of a Grade I or germinal matrix hemorrhage. Here you see the normal caudate, the normal thalamus, the bright Chorid plexus which is another vascular spot and the germinal matrix hemorrhage with a large increased echogenic mass in the area of the germinal matrix. This is an example of a Grade II IVH where blood is seen within the intraventricular space. Here you see on a sagittal view a normal size ventricle, a normal germinal matrix and blood layering out within the occipital horn of the ventricle. This is a Grade III IVH where the intraventricular blood is accompanied by dilation of both lateral ventricles. And this is a Grade IV IVH where there is a large proportion of intraparenchymal blood, in this case there is also a small germinal matrix hemorrhage and a ipsilateral ventricular bleed.

It used to be thought that there is a progression of IVH grades such that Grade I leads to Grade II, leads to Grade III and leads to Grade IV; however this has been called into question. Here this film shows the evolution of the parenchymal bleed, here you see an intraventricular bleed and shortly thereafter was the development of a parenchymal bleed without extension of the intraventricular blood directly into that area of parenchyma. Then subsequently the parenchymal bleed got larger and the areas become confluent.

Grade IV intraventricular hemorrhage is also known as a hemorrhagic venous infarction. It turns out that Grade IV IVH is not a continuum after Grade III IVH but rather the result of venous infarction. So here is a pathologic example of a large germinal matrix bleed with some intraventricular blood compressing the terminal vein which results in congestion of the veins draining the periventricular areas and venous congestion.
In this diagram you can see why it is called a hemorrhagic and venous infarction. Here is the medullary veins shown schematically draining into the terminal vein which drains right past the germinal matrix area, thus a large bleed in this area causes compression of this terminal vein which results in stasis in the medullary veins, rupture and a venous infarction. Thus there is not a simple progression from Grade I to Grade II to Grade III to Grade IV but rather any preceding level of Grade I bleed, Grade II bleed or Grade II can result in a Grade IV or parenchymal bleed. Pathologic consequences of IVH include ischemia, posthemorrhagic hydrocephalus and porencephalic cysts.

This is a MET MR spectroscopy of a baby who had a small germinal matrix bleed and what you could see is on the left side where there is no blood there is a very small lactate peak. On the right side where there was a small germinal matrix bleed there is a very high lactate peak indicating regional hypoxia and anaerobic metabolism.

Posthemorrhagic hydrocephalus. Posthemorrhagic hydrocephalus accompanies about 20% of Grade II IVH and about 40% of Grade III IVH. So here is the evolution of posthemorrhagic hydrocephalus, this baby had a Grade II to III IVH detected on the initial cranial ultrasound. Within a few days there was dilation of the ventricles on both sides, both ipsilateral and contralateral to the initial bleed. Over time the ventricular dilation became more and more impressive, you could see the resolving intraventricular clot right here and the baby underwent MR scanning in which you can appreciate the significant degree of ventricular dilation accompanied by resolving intraventricular blood.
This slide shows a study that detailed the evolution and treatment for posthemorrhagic hydrocephalus. In this study by Brouwer et al there were 94 babies who had a Grade III intraventricular hemorrhage. Of these about 1/3 died, almost 2/3 developed posthemorrhagic ventricular dilation with the need for intervention and about 16% required no intervention either because they did not develop posthemorrhagic ventricular dilation or they developed posthemorrhagic ventricular dilation that did not require treatment. Of the babies that required intervention 43% had lumbar punctures only, 55% had lumbar punctures followed by reservoir placement and one baby had the placement of an external drain. Of babies who had reservoir placement and the external drain 11 went on to require a shunt for a total of only 21% of all babies requiring permanent ventricular diversion.

The final pathologic consequence of IVH is porencephalic cysts. Here is a head ultrasound from a baby at 2 days of life who developed a bilateral intraventricular blood with the presence of an intraparenchymal bleed. On follow-up scanning 2 weeks later you can see evolution or resolution of the intraventricular blood with clot retraction but the presence of fluid within the clot area replacing normal parenchyma. At 40 weeks corrected this baby was severely hypotonic. At 6 months the baby showed a hand preference and by one year hemiplegia was diagnosed. At 2 years the baby underwent an MRI and you can see a large frontal porencephalic cyst at the site of the initial Grade IV IVH on the right, and a second porencephalic cyst was seen at the site of left occipital infarct which was not seen on the initial ultrasound but had been seen on an MRI performed at 35 weeks postmenstrual age. This child went on to walk unaided at 2 years of life and at 4 years he had good
right hand coordination but a residual left hemiparesis. So this baby had a good outcome and the reason is despite these large porencephalic cysts the baby had a very normal left frontal cortex and a very normal right occipital cortex and the plastic brain of the preterm baby is able to accommodate for many deficits.

Why does IVH happen? It relates to particular vulnerabilities of the preterm infant including both anatomic and physiologic factors. The germinal matrix is the source of all developing neurons and glia. Neurons develop in the germinal matrix and then migrate out along the radial glia to the cortex. The germinal matrix is located beneath the ependymal lining of the lateral ventricles, it has a rich vascularity in order to support the developing neurons. The vasculature of the germinal matrix is similar to venules, they are dilated with very thin walls, there is very sparse stromal support and it lacks features typically found in the blood-brain barrier. There is very little basement membrane and what is there is both thin and discontinuous, there are very few tight junctions and these are few and short and there are very few astrocyte foot processes thus there is incomplete envelopment with these foot processes. Thus these blood vessels are very easily ruptured.

Physiologic factors relate primarily to control of cerebral blood flow in preterm babies. Cerebral blood flow can increase in the presence of hypoxia and hypercarbia, it can decrease in the presence of hypocarbia and hypotension and there are frequent fluctuations in cerebral blood flow related to blood pressure and stability and absent cerebral blood flow autoregulation in the preterm infant.
The perinatal risk factors that increase the risk of IVH include any condition that alters fetal and newborn hemodynamic stability including both inflammation and infection, and obstetrical accidents including abruption, cord prolapse and any perinatal acidosis. Neonatal risk factors include any neonatal disease that results in hemodynamic instability including the presence of respiratory distress syndrome, in particular the presence of pneumothorax, the presence of patent ductus arteriosus and neonatal sepsis. Infants with these disorders are more likely to be hypotensive and acidotic thus they are more likely to receive volume resuscitation thus more likely to have fluctuations in cerebral blood flow and rupture of the fragile germinal matrix vessels.

Clinical presentation of IVH occurs in three different syndromes. The first is the silent syndrome, the time course of this is unknown, there are no neurologic signs and no systemic signs and these are picked up as incidental findings on routine screening cranial ultrasounds. The second is the saltatory presentation which evolves over hours to days. The infant may manifest hypotonia, apnea, altered consciousness, decreased movements or abnormal eye movement but system signs are minimal. And the final presentation is the catastrophic presentation. These are bleeds that evolve over minutes to hours, the baby will present with stupor or coma, hypoventilation, apnea, seizures, posturing, fixed pupils and perhaps flaccid quadriparesis. This baby would be hypotensive, bradycardic, have a dropping hematocrit, a bulging fontanel and significant acidosis and many babies with a catastrophic presentation do not survive their IVH.

We looked at the incidence of IVH at Magee Women’s Hospital in 780 infants born over a 3 year period at less than 32 weeks gestation. Of these babies 68% had no IVH, 20% had a Grade I IVH,
4.3% a Grade II, 3.4% a Grade III and 4.6% a Grade IV IVH. You can note that although all these babies were less than 32 weeks the average age of presentation decreases with the increased severity of the bleed such that the babies with no IVH averaged 28½ weeks and the babies with Grade IV IVH averaged less than 26 weeks gestation. Also note the significant increased mortality associated with the higher grades of IVH.

Treatment for IVH is primarily supportive and includes supporting blood pressure and respiration, transfusing if anemia develops and managing seizures and hydrocephalus. Because there is no clear treatment for IVH efforts are directed at preventing IVH. Many, many things have been tried in order to prevent IVH and very few have been successful. The two that have been successful include antenatal steroids and postnatal indomethacin. Antenatal steroids reduce the incidence of RDS and pneumothorax, they reduce the incidence of patent ductus arteriosus and with these there is less hypotension and less need to treat the hypotension therefore less fluctuations in blood pressure. However antenatal steroids also have an independent effect on reducing the incidence of IVH.

Postnatal indomethacin reduces patent ductus arteriosus, reduces episodes of hypotension and therefore less need to treat the hypotension and less fluctuations in blood pressure; however indomethacin also has an independent effect on the rates of IVH, it improves both the control of cerebral blood flow and strengthens the germinal matrix vasculature by unknown mechanisms. The bad news is that reductions in Grade III to IV IVH have not changed the long term neurodevelopmental outcome of the majority of preterm babies.
Moving on to periventricular leukomalacia, PVL occurs in about 5 to 10% of infants born less than or at 32 weeks gestation. PVL revers to necrosis of the white matter, anterior and lateral to the lateral ventricles in the brain, it is usually bilateral and symmetrical. PVL predicts the occurrence of cerebral palsy more reliably than does IVH.

Again we looked at the incidence of PVL at Magee Women’s Hospital, this data is over a 4 year period of babies less than 32 weeks and there were 1,667 babies included. 94% did not develop PVL, 1.9% had something called transient periventricular echogenicity which I will explain shortly, less than 1% had persistent PVE and 3.4% had cystic periventricular leukomalacia.

Interestingly we looked separately at babies diagnosed with an inflammatory bowel condition called necrotizing enterocolitis, these babies had a higher incidence of PVL. Of 62 babies with NEC were tested for 82% of NEC babies, of these 5.8% had transient PVE, 2% had persistent PVE and almost 8% had cystic periventricular leukomalacia. Now for this study the head ultrasound and the timing of the head ultrasounds relative to the onset of NEC were not necessary sequentially so this is more an association than a cause and effect. This is what the pathology of PVL looks like, here is the lateral ventricle, here is some cysts adjacent to the lateral ventricle and you can appreciate the liquification or necrosis in this area of cyst formation. On ultrasound this is how it appears. Here is the lateral ventricles and two large cysts adjacent to the lateral ventricles.

Now when we look at the head ultrasounds of babies we also scan in different planes and this particular baby that looked like simple cysts in one view had actually diffuse white matter necrosis
on another view. And here is the sagittal view where you can see this large area of cystic necrosis adjacent to the ventricle in the periventricular white matter.

Early on PVL may look like increased echogenicity so this is a baby who has increased echogenicity or PVE. Here you see the lateral ventricles and here is the areas of increased echogenicity or this bright white appearance. This bright white appearance indicates cerebral edema, when the edema resolves you may have resultant cystic PVL as in this case. On the other hand the PVE may resolve and the baby can have a normal outcome with restoration of normal appearance on the head ultrasound. If the PVE is persistent it increases the likelihood that there will be cystic periventricular leukomalacia and a poor outcome.

Consequences of PVL include white matter loss resulting in cerebral palsy and particular spastic diplegia, effects on the optic radiations including visual disturbances and grey matter loss resulting in both cerebral palsy and cognitive deficits. So here is a baby with PVL who at 34 weeks was significantly hypotonic with very poor head control, very poor body tone. By 40 weeks however this baby was already hypertonic, you can see the stiffening of the legs, the flexion at the ankles and the increased central tone.

This is spastic diplegia, the involvement of bilateral lower extremities with increased tone. In some babies it may manifest as increased tone at the ankles resulting in something as minor as toe walking to extension of the entire leg and if it starts to involve the hip muscles then you have scissoring. Note that the torso, arms and cognitive abilities of this baby appear to be normal. Why does spastic
diplegia occur? It has to do with the homunculus and the tracks that the fibers take to get from the grey matter down to the spinal cord. So here is a diagram of the way the white matter fibers pass through the periventricular region and you could see that the fibers going to the legs pass primarily closest to the ventricle in this area that we saw the periventricular leukomalacia. The trunk muscles are a little bit further out, followed by the arm, the face and the mouth. So in minor cases of PVL it’s primarily the legs that are affected, with larger areas involved then you have migration of the hypertonicity further up.

Here is an example of what might happen to the optic radiations when PVL affects the optic tracts. Here you see enlargement of the occipital horns of the ventricles indicating white matter loss in that region. You can see the grey matter coming right down to right below the white matter indicating less white matter in that area. If you did a retinal exam you would see large discs with large optic cups and a very thin neuroretinal rim indicating diffuse nerve fiber loss and the baby with this eye exam showed symmetric inferior visual field cuts.

This diagram shows the complex folding that the brain undergoes as the grey matter increases in size from 22 weeks gestation to full term. You see gradual, gradual increased folding of the brain in order to fit all the new grey matter within the confines of the head circumference. So it’s been noted on MRIs of babies who have PVL that periventricular white matter injury is associated with lower grey matter volumes at term gestation. So here you see that simplified brain of the preterm baby who does not have PVL. Note very little infolding in this preterm brain compared to the term baby who has a very complex interfolded grey matter indicating significant grey matter volume. This is
also seen in the healthy preterm infant when it reaches term who has the same sort of complexity of the grey matter. However in the baby who had PVL as a preemie who then reached term you see the more simplified pattern with less grey matter, less infolding and less grey matter volume.

This can also be appreciated on the coronal view where here is the preterm baby with the simplified brain with very little infolding, here is the healthy term baby with significant infolding and a lot of grey matter volume, the healthy preemie at term with appearance similar to that of the healthy term baby, and the baby with PVL at term who has less infolding, dilation of the ventricles, and overall less grey matter volume when measured volumetrically.

So why does PVL occur? Again there is a predisposition in preterm babies, it relates to both anatomic and physiologic factors. The anatomic has to do with the blood supply to the preterm brain whereas term babies have a deep watershed preterm babies have blood vessels that end right adjacent to the ventricles. Diagrammatically it looks something like this, there is blood vessels that penetrate into the grey and superficial white matter and there is long penetrators that end right adjacent to the ventricles. And it is hypotension and decreased perfusion to these areas that are thought to cause PVL. So in this study they injected the vasculature of the preterm baby with a die to make it visible and you could see the relative power of the areas adjacent to the ventricle indicating decreased perfusion to those areas.

Physiologically the preterm white matter has significant oligodendroglia growth and replication and these rapidly developing cells have a very high energy requirement. Because they have a very high
energy requirement they are particularly prone to hypoxic-ischemia in times of decreased blood flow. In addition preterm babies who are sick often have impaired cerebral autoregulation, thus the traditional model of PVL is one of hypoxic-ischemia where hypotension and hypocarbia result in decreased cerebral blood flow which result in periventricular white matter ischemia.

Newer theories however implicate inflammation in the pathogenesis of PVL. This stemmed from the epidemiologic observation that PVL is associated with chorioamnionitis, that is infection of the fetal membranes prior to birth with neonatal sepsis and with necrotizing enterocolitis. Increased cytokine concentrations can be found in the amniotic fluid of women diagnosed with chorioamnionitis, in the cord blood of babies born to women diagnosed with chorioamnionitis, in the cord blood of babies who go on to develop periventricular leukomalacia and in periventricular regions of the brain of babies with PVL.

The particular cytokines that have been associated with PVL include TNF alpha, IL-1 beta, IL06, IL-8 and IL-9. Here is an example of white matter in a baby with PVL staining for TNF alpha and all these cells increased staining for TNF alpha indicate inflammation in that area, and you could see that the TNF alpha is being produced by both astrocytes and microglia.

So why do cytokines cause PVL? There are a few possible mechanisms. One is direct toxicity of the cytokines, next cytokines are associated with regional inflammation and regional ischemia and finally cytokines may result in systemic hemodynamic alterations that result in global ischemia.
Thus cytokines being produced by both white cells and neurons, glia may be the common final
pathway linking hypoxia ischemia and infection inflammation in the pathogenesis of PVL.

So I’ve seen a few babies who have relatively good outcomes despite the presence of these
significant brain lesions but there are many babies who have poor outcomes. In particular risks are
the babies who have both IVH and PVL in combination. Here is a head ultrasound acutely obtained
in a baby who you see both an intraventricular hemorrhage and increased periventricular
echogenicity. Over time you see periventricular cyst formation, resolution of the intraventricular
clot, but the presence of ventricular dilation. And this baby at 36 weeks was already very
hypertonic, you see increased tone in the lower extremities with upgoing Babinski signs, increased
arm flexion and splaying of the fingers and by 18 months this baby demonstrated abnormal eye
movements, unable to sit unsupported, severe head lag and by 3 years the developmental deficits are
obvious.

In summary, improvement in perinatal and neonatal care have improved survival of very low birth
weight infants; however IVH and PVL remain significant morbidities. Improved understanding of
the pathophysiologic mechanisms of brain injury in very low birth weight infants may lead to novel
prevention strategies. Current research efforts are directed at the role of infection, inflammation and
cytokines in producing these brain lesions. Thank you.