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Forum

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The Chemotrode

Chapter Two

by Robert J. O'Connell

Eileen and her husband William sat quietly in Dr. Jack Neville's office Thursday afternoon at 3:10 holding hands but not speaking as they awaited the return of the Doctor. He had just left to retrieve the MRI scan of their sons John's brain from the file center outside his office. He returned with a patient file and a large envelope which contained a sheet of film which when removed from the sleeve appeared black. He clipped it to a light box hanging on the wall next to his desk. Turning on the light revealed a regular series of glowing pictures which appeared to be oval slices through an onion or some other layered structure. He picked up a pencil from his desk and used it as a pointer to examine carefully each of the sections of John's brain illustrated there. Humming to himself he placed a second film from a folder on his desk next to John's. Then he sat at his desk and studied the computerized lab report already in John's file.

"All right, I can now answer the most important question you have; I am convinced from these test results that John's problem is a form of Lissencephaly or one of the smooth brain syndromes."

Eileen and Bill both took a deep breath as Dr. Neville continued.

"We are still learning about these abnormalities and for some we are near imagining experimental techniques that hopefully will minimize the problems they create. Many smooth brain newborns initially look and act the same as children without a serious problem. This occurs because most newborn behaviors such as sleeping, sucking,

crying and pooping are controlled by lower brainstem centers which are probably normal."

"Oh yes, he was a wonderful newborn with a great appetite. And he was never fussy. My mother is still complaining that it was not fair for me to have such a quiet child when I was very noisy and colicky when I was an infant. But I can tell you now that I would rather have had him with a normal brain even if it meant he would be crying all the time. Although it is hard to judge now, I know that there is a very nice little boy in there waiting to come out and play."

Nodding, he said "But as you have correctly seen, latter in life, near his current age, parents begin to notice certain defects in movement, attention and visual tracking. These more complex behaviors depend on normal cortical function which is compromised in ways we still do not fully understand in the smooth brain child."

Eileen's teeth were clenched and her eyes were squeezed tight. After a moments hesitation she turned to face her husband, opened her eyes and asked, "Doctor what did I do wrong? I was so careful when I was carrying him."

At this Bill wrapped her in a big hug and made shushing noises as though to calm her obvious distress.

Jack said, "I am sure that you didn't do anything wrong. The results of John's blood test shows the presence of a defective gene that we believe is responsible for this defect. At least it is one I find regularly in my smooth brain patients. There is no indication that prenatal events could have caused this defect."

"But something else must have happened" she said, nervously adjusting her skirt as she squirmed in the chair to face the Doctor.

"Well yes, something happened, but there is no evidence that it was under your voluntary control. But there is a small possibility that the defective gene was inherited from one of you. We still do not understand the type of inheritance involved in this disorder so when we finish here I will give you both an order for a blood test that you should take to the basement laboratory today." He handed Bill the laboratory requisitions already filled out.

"Let me tell you our current ideas about this disorder."

"Please tell us everything; Dr Russell, our pediatrician said that you were an expert in neurology and a good teacher."

"Thank you for sharing that confidence but I am sad to

say that as of today we only have a general notion about human brain development so there is not that much specific to a particular patient to teach. Many of the exact details are still being worked out. First, imagine how many billion of steps are required to go from a single fertilized egg to a whole baby. It astonishes me every time I deliver a normal newborn.”

“Well that is nothing compared to knowing for nine months that it is all going on inside your own body. With every twitch and funny feeling you imagine all sorts of things especially near the end.”

He continued, “From what little we understand, the problem probably began very early in your pregnancy, well ahead of any ability you might have to feel wrong steps. Each of the necessary developmental choices follows a set of instructions carried in John’s genes. Included with these instructions are a set of master genes which provide the machinery needed to read the instructions and to make the tools used to carry them out.”

Bill stated, “So John has a broken gene somewhere and he might have gotten it from us.”

“Well in order to answer that we will have to wait for the results of the blood tests. Regardless of how it was obtained we are still trying to figure out if this particular gene carries wrong instructions or if the tools necessary to carry them out are wrong. In Lissencephaly we think that it is the latter. We do know that the brain of the early human embryo starts as a simple hollow tube. This is common for all vertebrates. It is packed with neural stem cells mostly located in the inner or ventricular zone of this tube. When these are properly stimulated, they divide over and over again to produce billions of daughter cells each of which can become an individual nerve cell.”

She nodded eagerly, “Yes, I learned this in one of my early pre-med courses”

Bill looked back at Eileen and smiled proudly.

The Doctor responded, “Then you already know that each of these new cells normally develops three regions, each specialized for a particular function. The cell body contains the cell nucleus with all of the genes and other synthetic machinery. This is where most new proteins and other secreted compounds are made. At one end of the cell, the axonal region grows as a thin process which moves through the brain tissue seeking contacts with appropriate neurons in other parts of the developing brain. The third region of the new neuron is a branched structure usually opposite the axon called the dendrite. It

is specialized to receive connections from incoming axons of other growing neurons. In this way the cells begins to form neural circuits with other neurons. These circuits are the building blocks of a normal brain.”

“I understand all of that but what was it in John’s development that was abnormal.”

“Well we imagine that each of the new neurons normally has a full complement of genes that, when properly activated produce all of the neuron types that make up the mature brain. In response to the appropriate chemical environment some of these cells acquire the machinery which allows them to move and they too begin to migrate through the expanding substance of the brain to find a new home in a particular portion of the expanding brain such as in the outer surface or cortex of the tube. There they grow axonal processes that have receptors to detect their appropriate partners in other deeper parts of the brain. They also make receptors on their dendrites which match up with axons from other regions to complete the necessary circuits. These steps are individually controlled and regulated by proteins and other secreted substances that are made in the cells. The pattern of these compounds expressed both spatially and temporally determines uniquely the capabilities and functions of the mature neuron. Of course, this modulation depends on the presence of appropriate genes in each of the neurons. As I said earlier, John has a defective gene.”

She said, “I understand most of that.” And repeated, “I was a pre-med major in college before I was married,” as though to convince the Doctor that she understood and to urge him to tell her more. “But where was the problem?”

He said, “Well it is difficult to be more precise or to tell you much more as we are still learning about brain development. But as I evaluate more and more patients with this disorder, it does appear that there are several forms of Lissencephaly with different degrees of severity. As John appears to be a complete little boy it is unlikely that he has the most severe form of the defect as that often involves genital abnormalities”.

She smiled, “Yes he is a normal boy, that is one of the first things that my husband checked before John was taken to the nursery.” Bill smiled and nodded as he acknowledged his interest in the correct equipment.

Doctor Neville continued “Most forms of the disorder have a genetic basis, involving one or more defective genes. With modern imaging and genetic techniques we are beginning to understand these defects and to identify which genes are involved, but we are far from understanding how these defects lead to the abnormality.”

Shaking her head she said quietly “But I still don’t understand where it went wrong?”

“Dear, given the complexity of the chain of events that make up the normal process of brain development, it is easy to appreciate how many different defects might give rise to the final abnormality. So first of all, I want to emphasize again that it very unlikely that you did anything wrong during your pregnancy. So do not waste your energies blaming yourself for causing this problem.”

Smiling she said “Thank you for saying that, as I am sure that my husband’s mother will continue to have something harsh to say about how our busy modern life style must have caused this. She didn’t think I was good enough for her boy and then that it was proper for me to stay in School after our marriage. But now we don’t let her old-fashioned ideas regulate our life. In fact, if it hadn’t been for her interference we wouldn’t have broken up in the first place and I probably would have been pregnant a year earlier. It took us that long to come together as a family and to force her out of our business. What can I do now to help John, I love him so.”

“Eileen, before we get to that let me first show you what John’s smooth brain looks like when compared to a normal infant of the same age.”

Eileen stood at the Doctor’s shoulder and peered intently at the two films. William remained seated but too stared up at the light box.

“These two sets of scans are arranged in the same order as they progress through the brain so that each slice in the same position on the two films should be comparable to each other. As you can easily see here on the left, John’s brain is smaller than the normal child’s here on the right. John’s brain does not quite fill the cranium which is this bright outside line. Part of this is because the cortex, or outer layer of his brain is thinner, has fewer layers and is much less folded. This is most obvious here and here” Pointing with the pencil. “The result of this is that John has much less cortical surface to use than this other child. If you were able to open the skull and look at the surface of the two brains John’s would appear smoother. What this means is that his cerebral cortex is less well developed and has fewer completed circuits. It just is a less complex structure. How this leads to the behavioral problems he has is still to be determined.”

Eileen shook her head and said, “There is no doubt from this that John’s brain is different. But, how did it get this way?”

Jack continued, “Well, there is a lot more to brain development than what we talked about earlier. We know now that in addition to an enormous multiplication of cell types and numbers that underlies the growth and self organization of the brain, there is also a major paring down or death of neurons that are in the wrong place or that are connected incorrectly. This process of cell death is now known to be an active one. A neuron will kill itself if it winds up in the wrong place or is incorrectly connected.”

Eileen interjected, “So John must have had too much cell death and that is what made his brain too small.”

“Perhaps, but this cell death is not so simple. It is fundamentally a matching process where there must be agreement between what the activated genes in the neuron should expect to find in their environment and the actual situation that exists surrounding the cell. This too is manipulated by the presence or absence of appropriate secreted substances. We estimate that nearly half of the neurons initially born in the developing brain die to result in the formation of a properly wired brain. The final result of all of these billions of steps is the formation of a normal human brain. So it remains possible that the defect lies in either the initial growth of the brain or in the cell death pathway.”

Mrs. Kelly had paled noticeably during this latter explanation, “So you really don’t know what went wrong with John.”

The Doctor raised his smallish hands, palms up and shrugged his shoulders in a gesture that suggested both bewilderment and despair, “Well yes, as you can imagine, development is hard to study. I can’t take John’s brain out to examine its microscopic structure so we have to use scientific imagery and our knowledge of development in other animals to imagine how human development works. It is easy to guess how a mistake here or there might be overlooked or corrected, but sometimes there are more major missteps.”

“At this Eileen stamped her foot and exclaimed, “Which is it for goodness sakes.”

William rises and puts a hand on her shoulder as though to calm her down.

The Doctor ignored the outburst and continued “I think that it is a two step problem. The most important factor involves a defect in the control of the number and placement of neurons that migrate from the center, ventricular region, to the outer edge of the brain to form the layers and folds of the cerebral cortex. An alteration in the layering of this region of the brain results in a

number of developmental defects that we collectively call smooth brain. I think that as a next step many of the neurons that should have reached the cortex or surface of John's brain get stuck in deeper layers where they cannot receive the proper connections from the axons of other neurons. Or because of their misplacement their axons cannot find the appropriate contacts with other neurons. Many of these misplaced neurons are then required to commit suicide because they have not made the right circuits with the net result that you can see here on his scan."

At this she sat back down next to her husband and embraced him.

Jack continued, "Looking forward, as a pre-med. major I know that you can understand the importance of developing a model system which will allow us to figure out the exact nature of the defect. Luckily, for the most part, the development of the brain of a worm or a fruit fly or a mouse or a monkey follows much the same path as the human and most often, when they are compared, directly we find that they use similar if not identical genes, proteins, and control substances. This biological similarity makes it possible for scientists like my self to engineer model organisms that mimic the human defect and in which experiments can be performed to try and understand a particular human disorder. In addition to my clinical practice specializing in children with Lissencephaly, I also have a small research laboratory at the medical school where we have a grant from the National Institutes of Health that seeks to understand the smooth brain problem. Our long term goal is to try to devise techniques which might fix them. At the moment, we have created a mouse model of the defect and are seeking a procedure that will fix mice with smooth brains."

"Oh" she exclaimed, "my biology professor in college had a mouse colony. He was interested in studying aggression so we were allowed to handle some of the mice every day in an attempt to make them gentler. Most of my girlfriends thought that it was gross, but I liked playing with them and watching them change"

The Doctor said, "We are still a long way from testing what we find to see if it will work in humans. In part, we have to determine that the mouse model actually mimics the human disease and then we have to see if the repaired mouse brain is actually normal. This requires information about how human and mouse brain development works. So far the match has been pretty good. But we already know that the development of the mouse brain is not identical to that of the human, given the outcome. If we remove or knockout the gene in the mouse that we think is responsible in the human, the

array of defects, or phenotype, we see in the mouse brain is similar to but does not match exactly the phenotype we see in the human. This too is not surprising given the differences in behavioral capabilities of the two brains."

She smiled uncertainly but with more hope in her eyes and said, "Will you show me what you have already done?"

"Yes, of course. But first I would like to know if you were willing to attend the next Lissencephaly Parents meeting. This is a gathering of families with Lissencephaly children that I host twice a year in the Medical School auditorium where we share insights and solutions to the problems that smooth brain children encounter as they get older."

"When is the next one?"

"Two weeks from Thursday at seven. After you have a chance to visit with them I would also like your permission to enroll John in my experimental clinical study of Lissencephaly. In exchange for this privilege I would continue to treat him without charge for the duration. As you might imagine this would be very useful for both of us. Once we get the results of your blood tests we will begin to understand the genetics and it might be possible to determine the risk of having another smooth brain baby."

"Oh yes, we want to attend the meeting and need the genetic information as Bill and I would like to have more children but we need to know if it is safe." They stood and quickly left the Doctors office to wait in the hall for the elevator to take them to the basement laboratory.

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