**SCHIZOPHRENIA - MY DEFINITION**

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**Schizophrenia is a polygenetic (over 100 identified risk genes) heterogeneous spectrum of psychotic disorders that are neurodevelopmental and when not optimally managed neurodegenerative.** It is a neurological syndrome. 5 usual domains of this illness include the positive symptoms (delusions and hallucinations), negative symptoms (flat affect and lack of motivation), cognitive symptoms ( decreased memory and reasoning), mood symptoms (emotional dysregulation, depression, and ultimately suicide), and commonly substance abuse ( “self-treatment” cannabis and cigarettes). Untreated schizophrenia is a chronic psychotic state. Psychosis is a detachment from reality resulting in a marked diminution in function and an inability to live a life of purpose and meaning.

**Often in the same family you will see other neurologic illnesses such as attention deficit disorder (ADD), bipolar illness, and autism spectrum disorders.** These less affected individuals were often spared some of the genetic risk and/or were not subjected to other stressors in life from conception onward (trauma, infections, drugs) that turn on at risk genes (genes that cause no harm unless activated). The phenomena of turning on at risk genes without modifying their genetic code is called epigenetics.

**Schizophrenia is a disease of gating. Gating is the ability of the individual to be able to focus attention and at the same time tune out extraneous stimuli internal and external.** Without gating people are continuously flooded by stimuli. During childhood they are less social and have attention deficit disorders. No matter how hard they try, their minds remain jumbled. With this “unquiet mind” they are increasingly “stressed” so that there is an inappropriate fight or flight response physiologically resulting in appropriate dopamine signaling. During adolescence, this entire process accelerates. A normal part of neurodevelopment is the removal of extraneous nervous tissue termed synaptic pruning. Unfortunately, commonly there is over-pruning. Important neural networks are disrupted, gating worsened and stress accrues leading to further dopaminergic dysregulation and the positive symptoms of hallucinations and delusions. With the ongoing diminution in gating the negative symptoms such as avolition and social isolation appear, and cognition declines. All this leads to the “break” from reality. Often during this time patients begin smoking cigarettes in an attempt at self-medication and improved gating. Others try to quiet their minds with marijuana. Cannabis in these susceptible individuals (epigenetic trigger that increases the risk of psychosis 5-fold), further exacerbates the psychosis.

**Schizophrenia therefore is a disease that starts before birth**. For example, the gene that encodes the alpha-7 nicotinic receptor is responsible for the full neurodevelopment of the brain’s “operating systems.” The alpha-7 nicotinic receptor is positioned after birth on inhibitory interneurons that are responsible for turning on and off neurons. This on-off switch is a critical component of the gating mechanism. As sensory input comes in from a variety of sources interneurons will shut down neurons that are processing the extraneous and turn on neuronal pathways that allow for focused attention. In patients with schizophrenia, this receptor system is not fully developed. From an early age these children will often be different in that they will have social anxiety, attention deficit and other behavioral issues. It is clear, that not everyone with this gene develops schizophrenia. However, if these same individuals are subjected to physical or emotional trauma from in utero to childhood, epigenetic triggers can give full expression to the illness. Even in individuals without obvious stressors, the illness may come to fruition. For instance, this can occur if they have other risk genes such as the overabundant synaptic pruning gene.

**Essentially these individuals were dealt a challenging hand**. Again, synaptic pruning is a normal stage of development during adolescence and ideally would rid the brain of neural pathways that are redundant or harmful and strengthen “good” pathways. The gene that results in over-pruning is responsible for the expression of complement. When this gene is overexpressed too much complement (C4a) deposits on neurons resulting in the microglia (the brains immune cells) destroying/pruning these cells. The pruning is often most extreme in the prefrontal cortex where most executive functioning occurs. In the general population, this gene by itself increases the risk of developing schizophrenia by 25 percent.

**The pathophysiology of Schizophrenia spectrum disorders provides a format for a reasoned approach to treatment**. We need to start at the beginning. We know that choline supplementation in pregnancy appears to improve the outcome of children who are at high risk of mental illness. Supplemented children have reduced rates of ADHD and social isolation in the first four years of their lives. The hope is that these children will have a reduced risk of developing schizophrenia. In rats, it has been shown that choline supplementation increases the expression of alpha-7nicotinic receptors. This results in normalizing neurodevelopment and normal gating. Four grams, twice a day of Lecithin (phosphatidylcholine) should become a routine prenatal supplement. Once the child is born attempts should be made to reduce possible epigenetic triggers. Inflammation is one of these triggers. For this reason, fish oil has been proposed as an early supplement in at risk individuals. One gram of fish oil is innocuous and something that has been demonstrated to decrease the progression of the prodromal syndrome to a schizophrenia syndrome.

**Finally, early intervention in psychosis is critical**. Inciting agents should be eliminated and agents that are effective at attenuating the syndrome should be used as early as possible. Clozapine, the most effective antipsychotic, for this reason should be used at the inception of illness. Clozapine has direct effects on the microglia, blocking the over abundant synaptic pruning, and has been shown to effectively restore alpha-7 nicotinic receptors at the interneurons. In expert hands optimal clozapine use often leads to improved gating, improved psychosis and ultimately to a life of purpose and meaning.