

Unkind Cytokines: A Journey from the Mind to Brain to Mind The Biological Basis of Depression

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Though this be madness, yet there is method in it.
Hamlet

The research that I have been doing with Doug Kerr and Chitra Krishnan has begun to shed light on the bad players in Transverse Myelitis, and this work, in turn, has led us to new ways of thinking about developing novel treatments. This work has also led us to new insights into the biology of depression and cognitive impairment. This research has implications for how we think about depression in Transverse Myelitis, Multiple Sclerosis and a number of other autoimmune conditions.

From the clinical perspective, we find depression associated with transverse myelitis and multiple sclerosis. Our preliminary research suggests that there is a 50% rate of clinical depression following the diagnosis of transverse myelitis; the relationship is not random. Fifty percent, or one in every two people, is a dramatic association. There are very few groups of symptoms that one in two people get, for instance, with multiple sclerosis, because it affects so many different parts of the body. What is going on with these disorders that the incidence of depression is so high? Is there some cause for the depression in TM and MS that might help us better under-

Figure 23. Death rates for leading causes of death among persons 25-44 years of age: United States, 1950-99

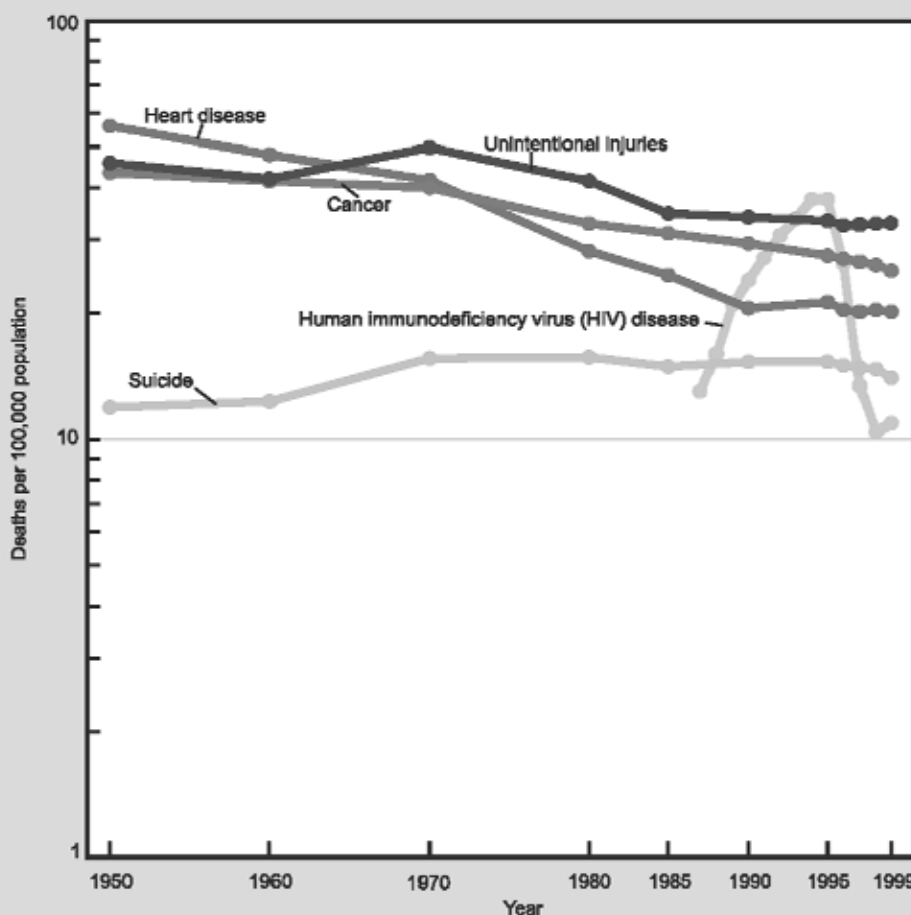


Figure 22. Percent of deaths due to leading causes of death among persons 1-24 years of age: United States, 1999

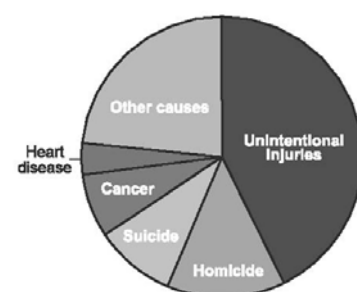
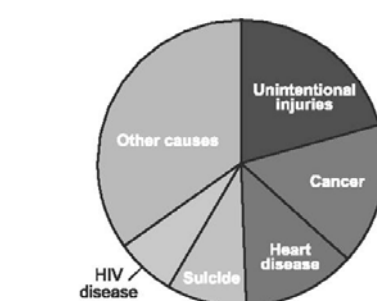


Figure 24. Percent of deaths due to leading causes of death among persons 25-44 years of age: United States, 1999



Health, United States, 2002 (US DHHS)

stand depression, in general?

These charts provide a good background and framework to understand the significance of our research. In a sense, this graphic represents a report card from the Department of Health and Human Services given to the medical practice of the United States

for the past 50 years. It is evident from this log scale that US medical practice has done quite well in some areas. There has been a 60% reduction in death due to heart disease since 1950. We have had a 40% reduction in death due to cancer. It is also important to keep in mind that we have invested billions of dollars in studying

heart disease and cancer. Deaths from unintentional injuries are down, and with the advent of highly active anti-viral treatment (HAART), deaths from HIV have also gone down dramatically. Suicide is the significant problem, the blemish on the medical profession's report card. Suicide is the lethal outcome of depression. Not only has suicide not gone down, since the 1950s, deaths from suicide have increased. Our question has to be why are we so far behind in taking seriously the issue of depression and suicide?

Unfortunately, one of the reasons that depression has not made the strides as some of these other conditions relates to the societal stigma that is attached to it. There are celebrities who have been willing to speak publicly about HIV, such as Magic Johnson, Arthur Ash, and Rock Hudson. There are very few people who have been willing to talk about their experiences with depression. When Brooke Shields discussed her experiences with post-partum depression, she was ridiculed, often with the complicity of the media, by Tom Cruise for doing so. So, stigma has played a role in the lack of focus we have placed on depression. Even though the rate of suicide as a cause of death in the DHHS report was lower than some of the other reported conditions, the numbers are not inconsequential. It is the fourth leading cause of death in people in the 25 to 44 age range in the United States, and it is the third leading cause of death in people up until the age of 24.

The definition and heterogeneous nature of depression makes it difficult to study from a scientific and clinical approach. The diagnosis of depression relies on the Diagnostic and Statistical Manual of Psychiatry (DSM-IV) criteria. A person must have five of nine symptoms for greater than two weeks to receive this diagnosis. The nine symptoms involve deviations in sleep (either increased or decreased), interest

Medical Causes of Depression:

Neurological disorders: CVA (25-50%), subdural hematoma, epilepsy (45-55%), brain tumors (30%), Parkinson's disease (30-50%), Huntington's disease (40%), syphilis, Alzheimer's disease (15-50%).

Autoimmune disorders: DM (30%), SLE (25-44%), RA (30-50%), **Multiple Sclerosis (37-62%), Transverse Myelitis (?)**

Drug induced: reserpine (15%), interferon-alpha (10-57%), β -blockers, corticosteroids, estrogens, benzodiazepines, barbiturates, ranitidine, Ca^{2+} -channel blockers

Substance induced (25%): EtOH, sedative-hypnotic, cocaine and psychostimulant withdrawal

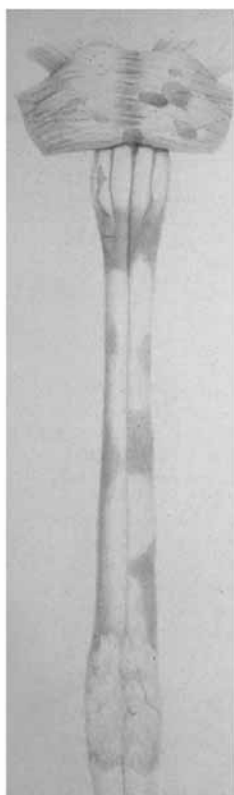
Metabolic: hyper/hypothyroidism, Cushing's syndrome, hypercalcemia, hyponatremia, diabetes mellitus

Nutritional: vitamin B12 deficiency

Infections: HIV, HCV, mononucleosis, influenza

Cancer (20-45): especially pancreatic CA (40-50%)

or pleasure, guilt or worthlessness, energy, mood (either sadness or irritability), concentration, appetite (either increased or decreased), psychomotor retardation, and suicidal ideation or thoughts of death. At least one of the symptoms must be decreased interest or low mood to make the diagnosis of clinical depression. The problem with this approach is that there are over 227 combinations to achieve the criteria of clinical depression using the DSM criteria. This represents a tremendous diversity of possibilities when characterizing depression. When a researcher is enrolling people into a study of depression, this means that we are potentially including 227 different types of patient presentations; presenting with 227 types of symptom combinations. This is a difficult problem for research on depression and for understanding depression. For example, I might enroll a person into my study who has sleep, interest, guilt, energy and mood problems. Another person may have problems with interest, concentration, appetite, psychomotor retardation and suicidal ideation. The only symptom they	share in common is trouble with interest; all of the other symptoms are different. However, they both are diagnosed with depression and they both are enrolled and included in my study. This is analogous to a scenario where I have a great antibiotic that I want to get on to the market for the treatment of pneumonia, and I enroll everybody who has a cough into my study. The problem is that cough is so non-specific a symptom; a person with a cough may or may not have pneumonia. The symptoms of depression are also very non-specific, and consequently, we are enrolling people into our studies with many different types of depression, and perhaps, many different kinds of conditions. To move our understanding and treatment of depression forward we must find a way of dealing with this heterogeneity problem.
	When I began to study auto-immune conditions, I was often asked by people what a psychiatrist with an interest in depression was doing focused on these conditions. My response was, "Why does Willy Sutton rob banks? Because that is where the money is."



Why do I study auto-immune central nervous system diseases? Because that is where the depression is. The frequency of people who have depression with one of these auto-immune conditions and inflammation in the brain is quite high. As a cause of depression, it is more important than a family history of depression and more important than child-rearing practices or experiences.

This is one of the earlier drawings of the lesions you get in the central nervous system of patients with MS. People with MS have the highest rates of comorbid depression compared with any other medical condition. It was with this background and understanding that I was first approached by Dr. Douglas Kerr who had recently initiated the only transverse myelitis treatment center in the world at the Johns Hopkins University School of Medicine. He asked me to get involved in his work. I indicated that I was focused on MS, because of the relationship between MS and depression (Patten & Metz, Psychother Psychosom, 1997, 66:286-92). The lifetime



prevalence of depression in MS is 37-62%, while it is 17% in the general population. The lifetime prevalence of cognitive impairment in MS is 45-65%. Depression is common in patients with MS and is associated with considerable morbidity and mortality. The available evidence suggests that depression in MS is caused by the effects of inflammatory insults to the brain. There is no genetic loading, there is no correlation with physical disability and periods of immune activation correlate with increased depression and suicides.

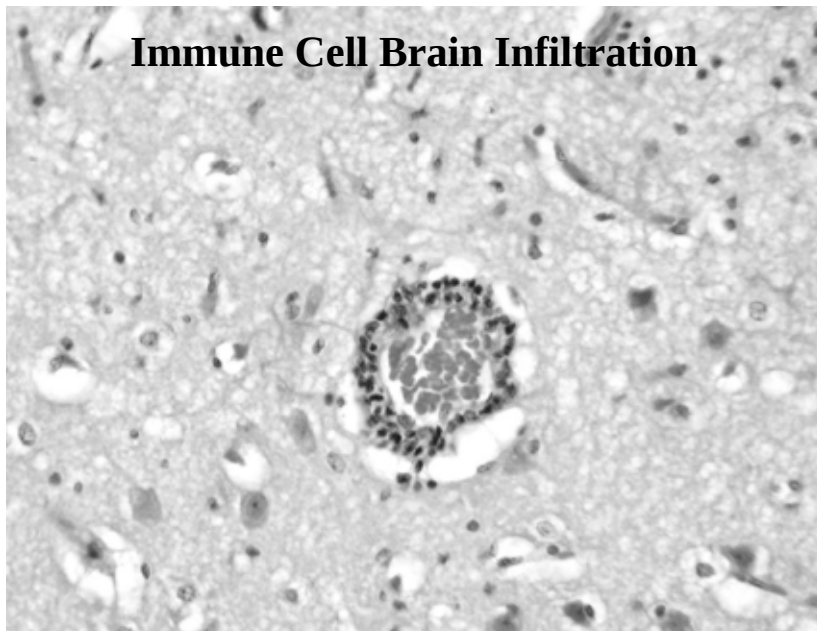
Dr. Kerr acknowledged at the time that there was very little known or understood about TM. He said that TM was sort of like MS of the spine; it is an autoimmune inflammation of the spine and the effect is across both sides of the spinal cord. It is immune mediated and the lesions in the spine lead to disability. It can impact motor and sensory function and it can cause bowel, bladder and sexual dysfunction. A third of the people get better, a third of the people have

some improvement, and a third of the people have a very bad outcome over time. Then he told me that many of the people with TM appeared to him to be depressed. My immediate reaction was that Dr. Kerr was confusing demoralization with depression. I suggested that there shouldn't be depression in TM, because the mood thermostat is located in the brain, not in the spinal cord, and TM was impacting the spinal cord. He pleaded with me to come to the TM clinic, make my own medical observations and lend a hand. I said that if I was going to get involved in evaluating patients for depression that we were also going to have to study transverse myelitis and depression so that we could understand what was going on.

We started screening patients for depression in the clinic; we evaluated consecutive patients who had multiple sclerosis and consecutive patients who had transverse myelitis. We compared these patients to averages that were already known using the SCL-90R depression screening test. The dark bar on the right for each category represents patients who scored in the 98th percentile and above; for example the 2% of the general population were very depressed. The 14% in the general population represents people who had mild-to-moderate severity in their depression scores. The 84% represents people who did not score in the depressed range. The known rate of depression in the general population is 5%. The number is between the 14% and the 2% you see in this bar graph, because some of the people who scored as being in the mild depressed range were demoralized and in distress but not suffering from a clinical depression since the SCL-90R is not specific for depression in this range.

For MS, the number of people who are depressed is between 8% and 31%; it has been reported to be 25% in cross section in numerous studies. What was shocking to us was that the TM

Immune Cell Brain Infiltration



tern of concentration and memory problems among people with TM. Again, these results suggested that, like depression, cognitive impairment was a marker of brain involvement in patients with TM.

We asked Dr. Carlos Pardo to study a pathological specimen from someone who had donated their body to science in advance of dying from complications of transverse myelitis. Dr. Pardo reported that there was inflammation in the brain that could be seen under the microscope despite the fact that the individual had a normal MRI of their brain.

This image is a section through the brain, not the spinal cord. This is in the parietal cortex region that controls, among other things, sensory processing. We should only be seeing lots of red blood cells in this image. The red blood cells all clustered in a capillary, a very small blood vessel coursing through the brain. The walls of the capillary should just be one cell layer thick. All of the dark nuclei clustering around are from what is called perivascular cuffing; it forms sort of a cuff around the vessel where there are activated, angry immune cells, white blood cells. This is exactly what you

see early on in multiple sclerosis before a brain lesion or MS plaque forms. They will then go on and develop into a lesion that can be seen on an MRI. You never see these go on to develop into lesions in an MRI with transverse myelitis. By definition, transverse myelitis means that you do not see lesions in the brain. But despite having a normal MRI of their brain, this suggests that there may be activated and aggressive inflammation going on in the brain of patients with TM that is below the level of detection by neuroimaging.

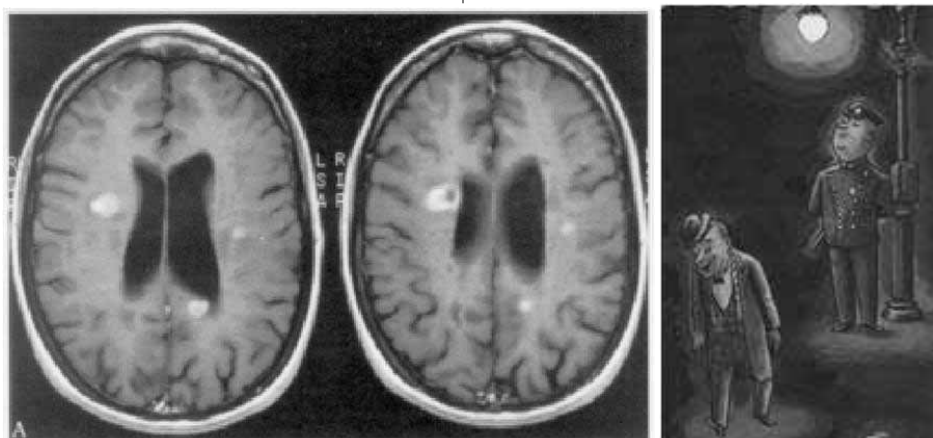
What is the key mediator of depression in MS: have we been looking in the right place?

A drunken man is searching under a

street lamp for a set of keys. A passer-by offers to help. Together they search and search in vain. Finally, the passer-by asks where the keys fell. The man points to the other side of the street. "Why are you looking on this side when you dropped them over there," the incredulous passer-by asks. The reply, "the light is much better here."

This joke effectively describes the problems that we believe have been encountered in research involving depression in multiple sclerosis. When you look at an MRI of the brain of someone who has multiple sclerosis, you see MS lesions or plaques. These are the light spots on the MRI. Everyone reached the same conclusion; depression had to be related to these plaques. Interestingly, however, the plaques do not correlate at all with depression. There is some weak association with the number of plaques, but this has ultimately proved to be a very poor correlation.

We now think that transverse myelitis is a much better model for studying autoimmune depression than MS. There are no plaques visible in the brains of patients with TM. Thus there is no confusion or distraction from these plaques in studying the way inflammation can impact the brain and cause mood dysregulation. People with TM have the same depression and the same cognitive impairment as seen in people with MS without any of the



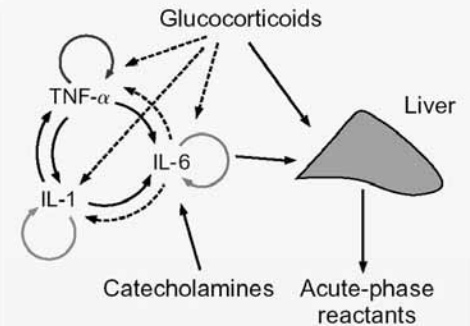
plaques. This suggests that there is something else going on that is causing depression.

When a person with TM has a lumbar puncture done, the spinal fluid is drawn with a needle that is inserted between the L4-L5 vertebrae. Interestingly, the lesion can be up in the neck area, and we still pull off white blood cells way down in the lumbar region that are markers of the immune activation which is occurring. The immune system has already gotten across the blood-brain barrier and is causing trouble. Dr. Kerr and I reasoned that if we are pulling off immune system cells from the lumbar region with a cervical attack, why can't the cells also move up or release something that would diffuse potentially into the brain.

The next step for us was to see what diffuses in the immune system. There

are a number of things diffused in the immune system, and one of the critical things is cytokines.

Cytokines are chemical messengers between cells of the immune system. Cytokines are the way one white blood cell is able to communicate with another white blood cell. This is a representation of a CD4⁺ T cell, the General Commander of the immune system. It is what it is taken out by HIV and when it goes, the whole immune system collapses and you get AIDS. It is the General, and to rally the troops, it releases all of these chemical messengers that sound the bugle. The bugle is what recruits all the other immune cells to get excited and start coming in and doing their job. Cytokines are the signaling messenger; allowing two white blood cells to communicate, much as neurotransmitters are the



Interactions among the Inflammatory Cytokines and the Effects of Glucocorticoids and Catecholamines (Review from the New England Journal of Medicine, Chrousos, 1995)

messengers for neurons. Cytokines diffuse through the body to call in help, the back-up forces and the reserves.

Amongst the cytokines that have already been implicated in auto-immune diseases, TNF-alpha, IL-1 and IL-6 have already been shown to play a key role in many illnesses, including arthritis. The image represents a joint and the cytokines are produced in response to the General CD4⁺ T cell getting over-activated. It is recognizing the joint as foreign and it releases these messengers that then cause these other cells to produce the pro-inflammatory cytokines; IL-6 being one of the three early cytokines that get released.

The involvement of IL-6 immediately raised my interest. Catecholamines (that comprise part of the fight or flight response) stimulate the production of IL-6; this means that stress plays a role in this system. Catecholamines include the stress neurotransmitters norepinephrine and epinephrine. That means that stress, which releases catecholamines, increases IL-6. IL-6 also stimulates the production of corticosteroids, which in humans is cortisol. Cortisol is the body's version of an endogenous glucocorticoid, which is in the same family as solumedrol and prednisone which are given to patients to treat immune over-activation. Cortisol is the

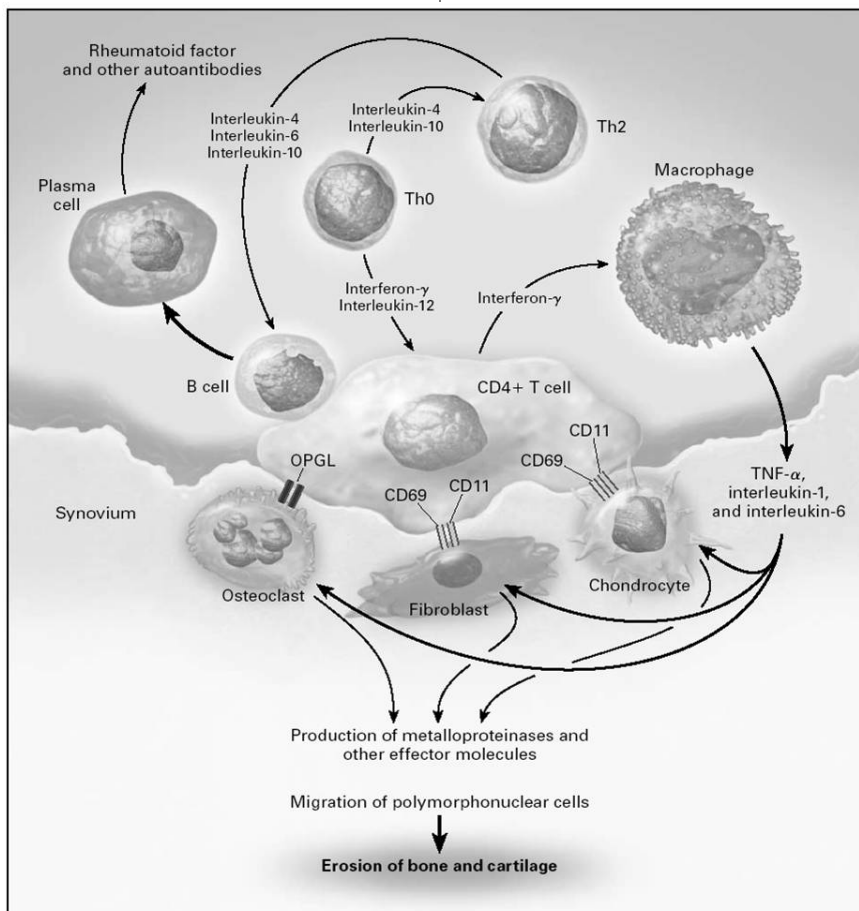


Figure 1. Cytokine Signaling Pathways Involved in Inflammatory Arthritis.

The major cell types and cytokine pathways believed to be involved in joint destruction mediated by TNF-α and interleukin-1 are shown. Th2 denotes type 2 helper T cell, Th0 precursor of type 1 and type 2 helper T cells, and OPGL osteoprotegerin ligand.

human version of an endogenous steroid, the version of the steroids that are produced by our bodies. We already knew that depression involved elevated levels of cortisol in the brain. In patients who are depressed, you can actually measure elevated levels of cortisol in their blood stream through a test called the dexamethasone suppression test. In 80% of people who are depressed, their cortisol levels are elevated compared to normal levels.

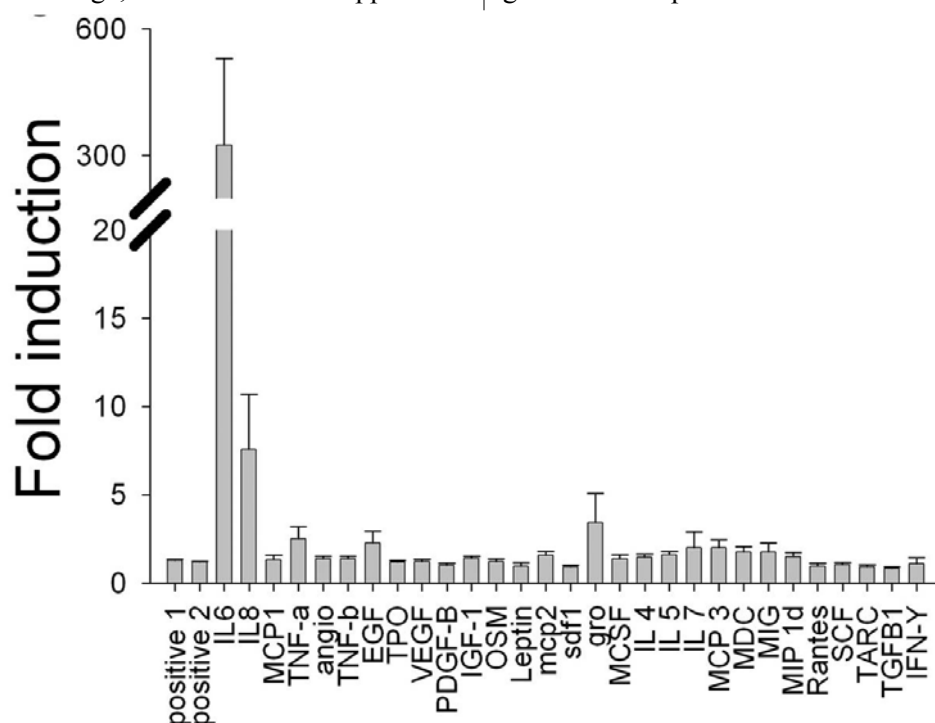
Thus, IL-6 is situated in a key location to permit it to play a key role in coordinating cortisol which is a marker of both stress and depression.

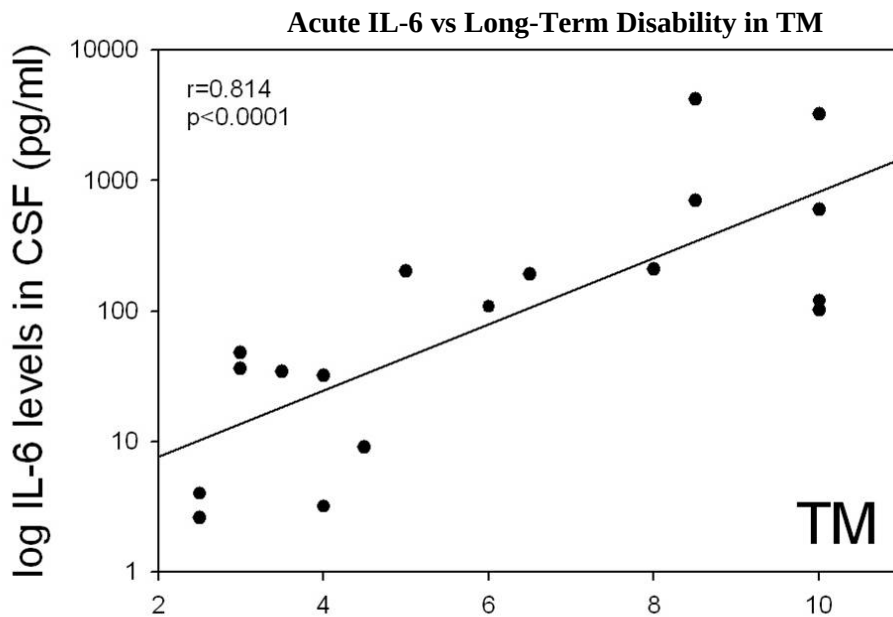
There is also independent evidence supporting the role of cytokines as a cause of depression. If cytokines, including IL-6, are given to animals, they get what is called sickness behavior; it is a syndrome that resembles the symptoms of depression in humans. It is referred to as sickness behavior, because there is no way of defining depression in a rat, for example. A rat with sickness behavior does not have an interest in doing anything. They are not social; they will not approach and socialize with another rat put into their cage; even those of the opposite

sex. Rats love saccharin; rats with sickness behavior are not interested in pressing a lever to get such a reward. They are not interested in feeling good. They get up and move around and they will go feed when they are hungry, but they have a lack of social interest in other rats or even in grooming themselves. They have this set of symptoms that you might imagine would look like depression for a rat. More direct evidence for the role of cytokines in depression comes from the observation that if you give cytokines to humans, they get depressed. Some of the early studies of people with cancer involved giving them cytokines to try and treat their cancers. Lo and behold, they got depressed. Another contemporary example involves the current treatment of hepatitis C. Patients are treated with interferon alpha which then goes on to elicit the production of these other cytokines, IL-6 being one of them, in the brain. Interferon alpha causes depression in 25% of the people being treated for hepatitis. People being treated for hepatitis C need to be monitored for depression, because 2% of them will go on to attempt suicide from this

treatment. Thus, we know that cytokines can cause depression in humans. We also know that IL-6 increases cortisol. Not surprisingly, if you give anti-depressants both to animals as well as to humans, the level of these pro-inflammatory cytokines and of cortisol are decreased, further implicating them in the pathophysiology of depression. There was enough smoke from what we observed and understood about cytokines for us to begin to study the cerebral spinal fluid of patients with transverse myelitis.

The results of this study are reflected on the scale in the graph. While we suspected IL-6 from our knowledge of prior research, we didn't want to bias ourselves in TM by investigating only this single candidate. We began a systematic study of 42 different cytokines in the cerebral spinal fluid of patients with TM. This graph shows 25 of the 42 cytokines that we analyzed. A one on the Y axis of this chart means that the ratio of levels of these cytokines in patients with transverse myelitis was the same as controls who did not have transverse myelitis. Anything above one meant that the TM patients had elevated levels of these cytokines. For instance, the graphic shows elevated levels of the cytokine IL-8 as compared to controls. One could conclude that an 8-fold increase is certainly worthy of following up and investigation. However, our attention was immediately drawn to the IL6 results. First, it is important to notice that this is a broken graph; the scale jumps from 20 to 300. There is not nearly sufficient space on the page to show the relationship between the levels of IL6 and the other cytokines that we analyzed. It is, on average, 300-fold elevated, not 20-fold and that result was absolutely staggering to us. In biology, you have interesting results and can publish a paper, if you see a 30% increase. This is a 300-fold increase, which corresponds to a 30,000% increase. In our wildest dreams, we hadn't anticipated such a staggering result.





We measured the levels of IL-6 in patients with transverse myelitis when they presented to the emergency room or came into the clinic acutely (e.g., shortly after the onset of their symptoms for the first time). We next determined their disability scores at follow-up (roughly 6 months after the onset of their neurologic symptoms) using the EDSS disability scale. Anything below four is still walking independently; ten means death, obviously the most severe outcome. The levels of cytokines and IL-6, in particular, correlated very nicely with the outcomes of these patients; with all of the patients who presented acutely with levels of IL-6 less than 50 pg/ml doing very well and regaining independent ambulation in follow-up.

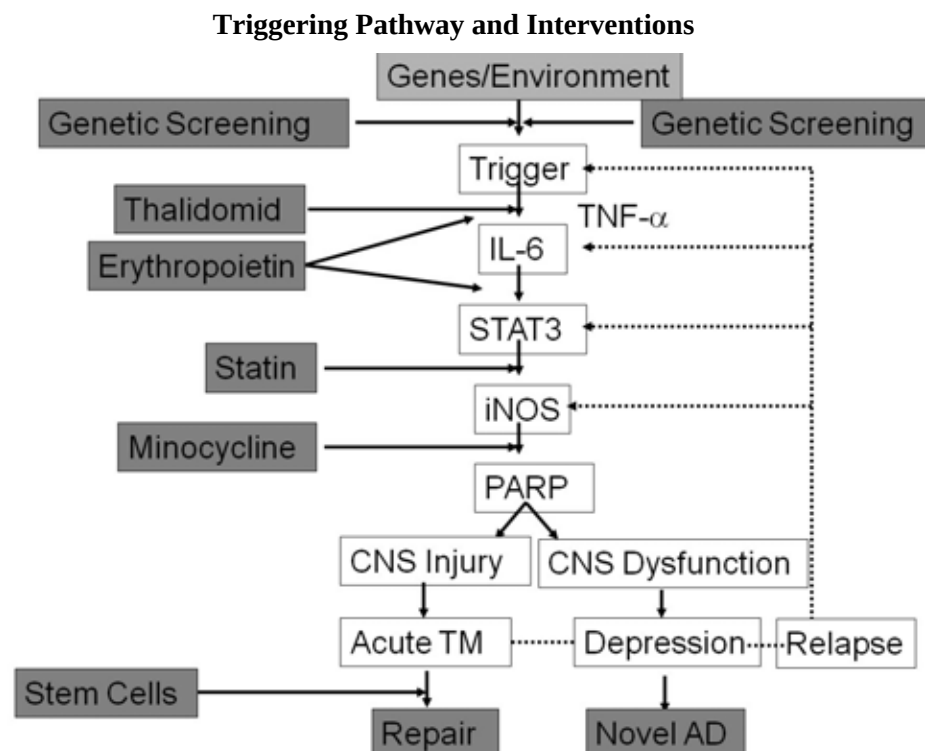
We conducted a study which demonstrated that IL-6 is both necessary and sufficient for the spinal cord injury found in transverse myelitis (Kaplin, et al. Journal of The Transverse Myelitis Association, Vol. 1, January 2006). If you take the CSF out of a patient presenting with severe transverse myelitis, and you put it on a spinal cord in the laboratory, it kills spinal cord cells. CSF from patients with TM is toxic to spinal cords, which is why it caused

the damage in the person from whom we took it. If you leave all the thousands of other proteins in the CSF alone and pull out only one protein, IL-6, it is no longer dangerous or toxic to spinal cords in the lab. Thus IL-6 is necessary to cause the injury to the spinal cord. IL-6 is also sufficient to cause spinal cord injury. When we infused IL-6 into the spinal

cord of rats, it caused paraplegia over the course of days. When the spinal cords from IL-6 treated rats are examined, they look pathologically like the spinal cords seen in transverse myelitis patients; they had the same kind of microscopic injuries that you see in transverse myelitis patients.

While we were studying depression, we quite accidentally solved one of the central mysteries in transverse myelitis; what causes the injury? What in the final common pathway of damage is the gun that the immune system uses to cause the injury in transverse myelitis?

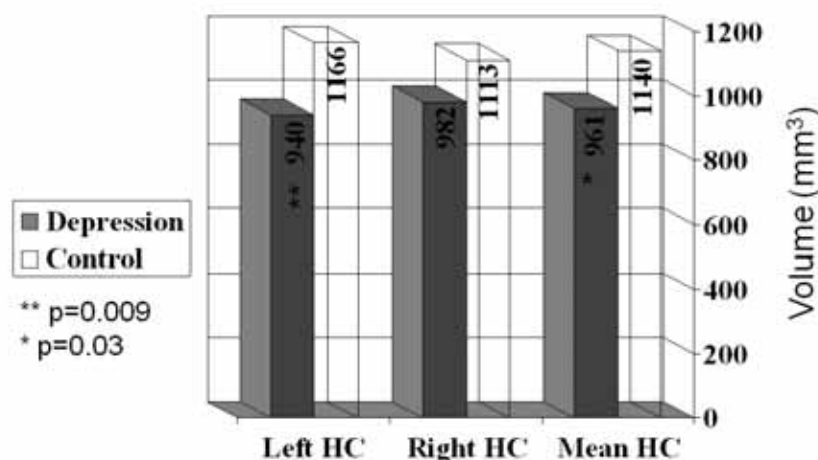
This was a tremendously important discovery. We then investigated how IL-6 caused damage to the spinal cord; specifically what chain of events or cascade IL-6 initiates that result in neuronal injury and dysfunction. We now know the whole signaling pathway that IL-6 uses to cause the injury in the central nervous system. Now that we know the pathway, we can begin to look for ways to intervene in this triggering pathway to halt the progression of the attack. This chart



shows some of the possible drug interventions and these are already FDA approved drugs for other applications. Minocycline is an antibiotic; it is also being discussed as a drug for multiple sclerosis. Erythropoietin and Statins are already being used in experimental protocols to treat MS, even though we do not know exactly how those drugs are working. Our work on IL-6 and its signaling pathway leads us to think they are blocking this simple pathway. We are starting a trial of Erythropoietin at Johns Hopkins as a neuroprotective agent during an acute attack of TM. The next set of studies might look at erythropoietin for people with recurrent TM. Once you know this triggering pathway for the inflammatory attack, we are off to the races in finding treatments that are already approved and we can begin to develop new treatments.

My chairman said, "That's so great. You did good work over there with Doug Kerr. But what have you done for me lately in Psychiatry?" In our excitement about uncovering the cause of tissue injury in TM, we had strayed from our original reason for starting these investigations. I said, "Oh right, psychiatry, I forgot." So, we returned

20% Hippocampal Volume Loss in Depression
(Bremner JD, et al, Am J Psychiatry 2000)



+No volume loss in amygdala, caudate, frontal or temporal lobe or whole brain.
 +Persisted after controlling for brain size, alcohol exposure, age, and education.

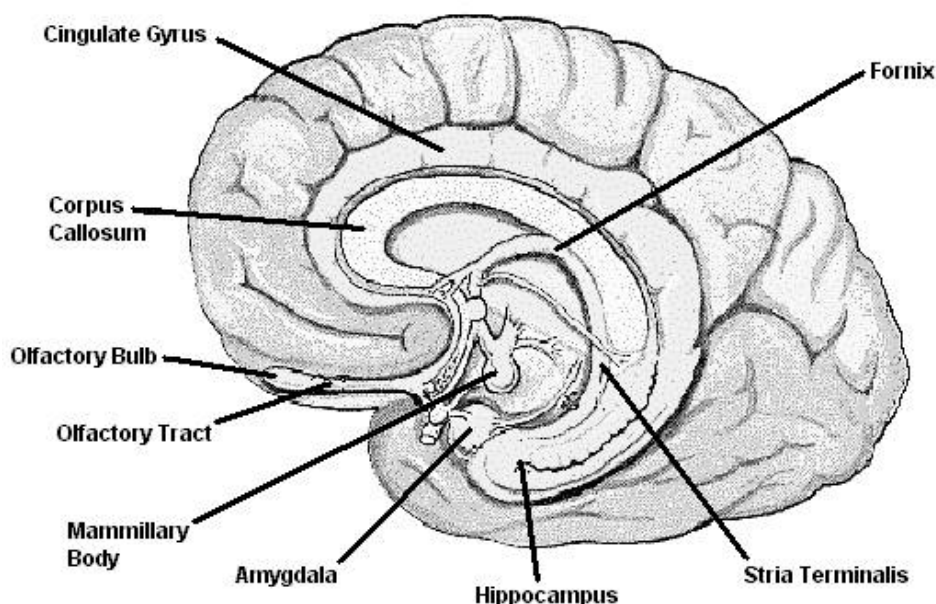
to the question of depression. Our next experiment involved looking at the effects of IL-6 on the brain. We used the same procedure and the same doses that we used on the rat spinal cords that caused injury to their spinal cords, and we infused IL-6 into the center of their brains. The rat's brains were fine. We looked at their brains under the microscope after the experiment and we could not see anything; there was no tissue destruction like we saw in the spine. I

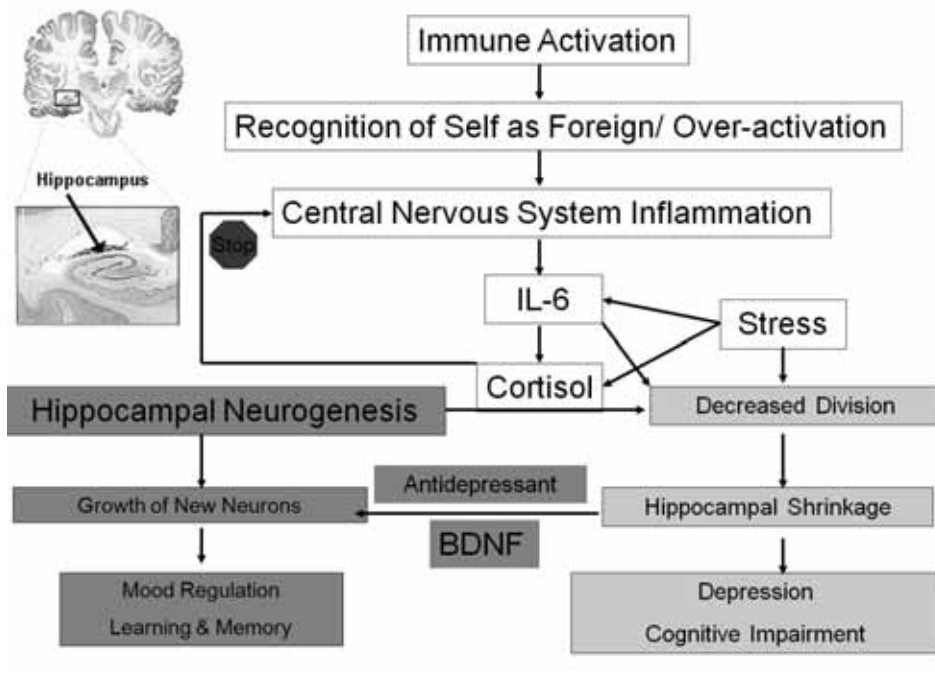
suspected that there had to be some kind of change, so we decided to look more closely to figure out what was going on.

This is the limbic system which starts off with the olfactory system. The limbic system is the seat of emotions. The emotional circuit of the brain starts in the nose. This is the reason the perfume industry is so successful; because our sense of smell really gets emotions going. From the olfactory system, it leads right into the limbic circuit and it goes all the way down to the hippocampus. Interestingly, the hippocampus is not only important in emotions, but it is important in cognition. In TM, just as in MS, as we have discussed, there is the risk of depression, as well as memory and concentration problems.

When reviewing the literature, other researchers have shown that in patients who are depressed, they have 20% decreases in hippocampal volume. The size of this region of the brain (hippocampus) shrinks over time, if the patient is not treated for depression. If the depression is treated, you prevent this shrinkage. The hippocampus is one of only two regions of the

Limbic System: Hippocampus as Seat of Cognition and Emotion





adult brain where new neurons are made throughout one's lifespan. The process is called hippocampal neurogenesis; neuro being neuron and genesis being birth. This is an interesting phenomenon for which there is a Nobel Prize waiting to be had for the person who figures out exactly how this happens and why this happens. There are new neurons being produced in the hippocampus throughout our lives. The function of new neurons in this region is not known. We know that depression and prolonged stress lead to hippocampal shrinkage and that it is prevented by antidepressant treatment, which may correspond to changes in hippocampal neurogenesis.

Interestingly, antidepressant treatment stimulates new hippocampal neuron production, one to two weeks after the initiation of therapy. Antidepressants have been shown to stimulate the production of new neurons in that region in a time frame that looks like it is consistent with the time frame for their onset of action for depression. When you first give them antidepressants, there is no effect in the first few days. Two weeks later, three weeks later, we begin to see the production of new

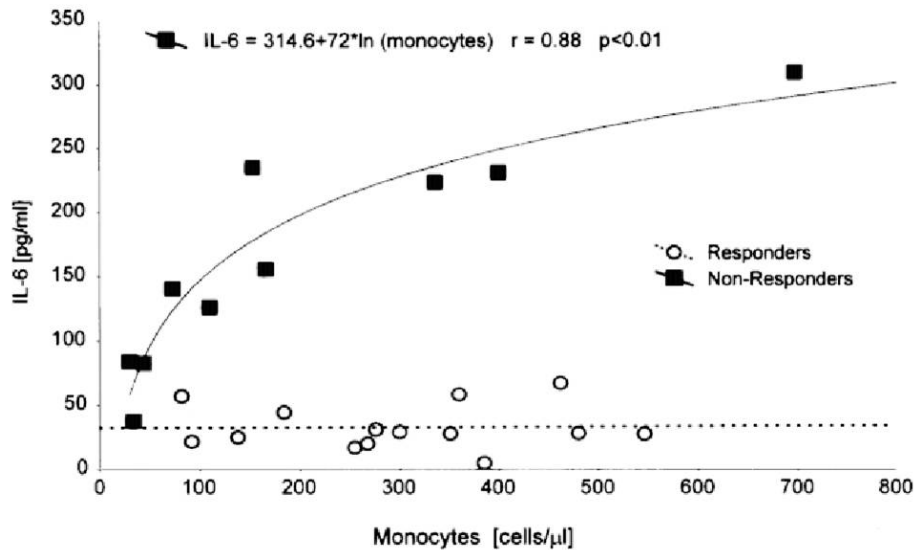
neurons. Coincidentally, it is in this same time frame that we begin to see people's depression improving. Finally, experimenters have recently shown in rats that if you block the production of new neurons in the hippocampus, antidepressants no longer have a behavioral effect on the rats that you can observe in the lab. When you give them antidepressants, it seems to calm them down and they are more relaxed and they will go out and feed in the light. Generally, rats and mice do not like to feed in the light; they like to stay covered. If you block the production of new neurons (hippocampal neurogenesis), antidepressants no longer exert their behavioral effects in animals and the animals will not become more relaxed even with the same treatment.

This research led us to focus on the hippocampus to look at the possible relationship between IL-6 and depression. We can introduce a marker (called BrDU) into the hippocampus that identifies only cells that are dividing; the marker is only taken up by these dividing cells. We introduced phosphate buffered saline into

the hippocampus of rats as a control; they continued to produce new neurons. When we introduced IL-6 into the brains of rats, they had virtually no hippocampal production of new neurons. IL-6 almost completely shut down the production of new neurons.

This graphic represents our current thinking about depression in TM and MS. There is immune activation that leads to the recognition of self as foreign; this is the central problem with all auto-immune diseases. This leads to the central nervous system becoming inflamed, and the activated white blood cells will release a lot of things, including IL-6. IL-6 stimulates cortisol. It is significant that the cortisol stimulation is not just random. Why does IL-6 produce cortisol? Why do we give people steroids when they have an MS attack or a TM attack? We give people steroids, because the body thought of it first; the body naturally produces cortisol to quiet down the immune system. The body has a reason for doing this. The problem is that there is an innocent bystander involved when the body does this under the threat of great or perhaps overwhelming inflammation. The innocent bystander is that the combination of IL-6, cortisol, and stress block the production of new neurons in the brain. We know from other studies that cortisol also blocks the production of new neurons independently of IL-6. Additionally, stress increases IL-6 and cortisol. Next, there is decreased production of new neurons in the hippocampus that leads to the hippocampal shrinkage. This is the model that accounts for what goes on in depression with a hippocampal shrinkage and that leads to depression and cognitive impairment. What happens when you give an antidepressant is that it produces new growth factors like brain-derived neurotrophic factor (BDNF). The antidepressant leads to the growth of new neurons and you can get mood regulation and perhaps some memory and concentration back.

IL-6 Production in Patients with MDD (Lanquillon et al, Neuropsychopharm, 2000)
Consecutive inpatient admissions; Treated with ATP (150-250 mg/day)



What I have just described for you is one of the first testable hypotheses for the biological basis of depression. We are currently in the process of testing this model. If we are able to prove the model, this will lead us to a whole new set of options to try to intervene to block or stop this process with perhaps more than current antidepressants. For

instance, we might consider the use of growth factors.

These investigations are important even for people who do not have transverse myelitis and multiple sclerosis. This graph represents a study done looking at patients who were treated with amitriptyline, which is a

tricyclic antidepressant, who did not have an auto-immune condition. It is interesting that many people got well when they were given this antidepressant, but some did not. What was the difference between those people who got well and those that did not? For those people who got well, their immune cells stopped over-producing IL-6 and those people who did not get well still over-produced IL-6. This may be the same thing going on for TM and MS, and for depression in general.

Researchers in our lab are currently studying Alzheimer's disease. In Alzheimer's disease you have a deposition of plaque which is called amyloid. Amyloid is like a sticky gum that gets into the brain. The graphic also shows microglia. Microglia are the clean-up crew for the brain. When they go in to clean this up, they start producing IL-1, TF alpha, and IL-6.

We are now studying the effects of IL-6 in that process. This graphic shows preliminary work that was done by Jennifer Cheng. This shows the IL-6 production taking white blood cells out of healthy controls (light lines). This is the IL-6 production in patients with Alzheimer's disease (dark lines). The graphic shows a complete separation;

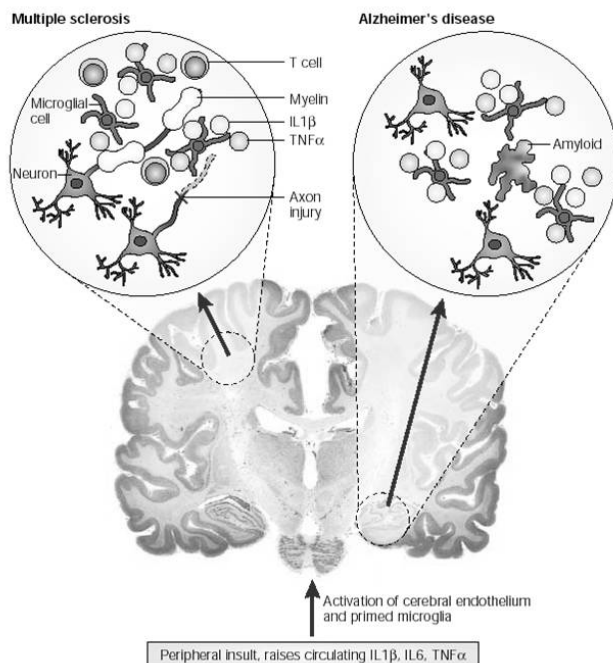
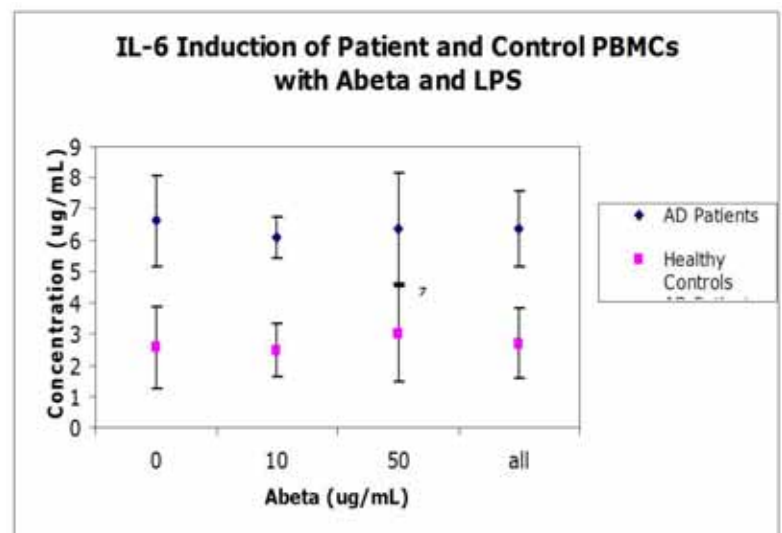


Figure 3 | Impact of systemic infection on the brains of patients with multiple sclerosis or Alzheimer's disease. In chronic neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis, peripheral insults that result in elevated peripheral cytokine synthesis can cause the activation of already primed microglia and lead to acute central cytokine synthesis with behavioural consequences. These cytokines, or other secretory products of the activated microglia, might cause axonal or neuronal damage and produce a lasting effect on the neurodegenerative process. IL, interleukin; TNF α , tumour necrosis factor- α .

Alzheimer's Disease Preliminary Results



the patients with Alzheimer’s disease made over twice as much IL-6. This means that we now have a potential marker for Alzheimer’s disease, as well.

We now have a testable hypothesis for what causes depression. This new model may lead to novel and more effective diagnostic and treatment methods. Remember, before we had an EEG, which is a novel diagnostic method for seizures, everyone thought that people who had seizures were possessed by the devil. There was a great deal of stigma surrounding seizures and a great deal of discrimination. Even in the 1960s in this country, many states had laws which required the forced sterilization of people who had epilepsy. With the advent of the EEG, the stigma was eradicated. Seizures became understood as a brain-based illness.

Our hope is that we will develop new ways for testing this pathway to help remove the stigma about depression and to help us find novel treatments. TM stands for Transverse Myelitis; but it also now metaphorically stands for Transforming Medicine. It is the only autoimmune CNS disease in which a single molecule is known to be pivotal in the course of the disease. This work has led us to a new way of thinking about depression and concentration and cognitive impairment problems. The development of novel treatments for all aspects of TM might not only improve the lives of patients impacted by this illness, but may help in the treatment of a wide variety of diseases.

COURAGE does not always roar.
Sometimes courage is the quiet voice at the end of the day saying,
“I will try again tomorrow.”

Mary Ann Radmacher
By way of John Craven,
Idaho Support Group Leader

Recruiting for Studies

**Recruiting for ACP Study:
Help us to Find the Causes and
Cures for T M , A D E M ,
N M O , M S and the other
Neuroimmunologic Disorders**
Jana Goins

The Johns Hopkins University is working in conjunction with the Accelerated Cure Project for Multiple Sclerosis (ACP) to conduct a large scale research study which will play an important role in determining significant causal factors and disease trends for demyelinating disorders such as Multiple Sclerosis (MS), Transverse Myelitis (TM), Optic Neuritis (ON), Devic’s Syndrome (NMO), Acute Disseminated Encephalomyelitis (ADEM) and other related diseases.

Several major academic centers located throughout the country will serve as coordinating project sites, creating a national network of collection sites. Study enrollment is targeted at 10,000 subjects over ten years. Enrolled subjects will be asked to contribute personal data (such as medical history and family information) and biological samples. The personal data collected from all subjects will be combined into a single database while the biological samples will be processed at a central laboratory and stored. The complete anonymity of study participants will be protected. The result will be the creation of a comprehensive information system and specimen repository from which researchers can request samples to conduct in-depth analyses on various disease aspects. This study will play an important role in increasing the current knowledge of demyelinating diseases and therefore aid researchers in the development of better diagnostic techniques and

cures for these diseases.

This is your chance to help! We are enrolling patients with multiple sclerosis, transverse myelitis, optic neuritis, acute disseminated encephalomyelitis, neuromyelitis optica (Devic’s) or clinically isolated syndromes (one demyelinating attack, but not fulfilling the diagnostic criteria for MS). Those who are currently patients at Johns Hopkins will be able to join the study without a referral from their physician, and will just need to contact the Johns Hopkins project coordinator for study enrollment information. Johns Hopkins patients who are aware of their next scheduled clinic date may get in touch with the project coordinator *before-hand* in order to schedule a study meeting during this clinic visit. Subjects participating at Johns Hopkins will be offered a \$25 check to compensate for lunch and parking on the day of the visit, but will not be reimbursed for any travel expenses. At this time, patients receiving care outside of Johns Hopkins may be subject to additional enrollment requirements.

Please note, the enrollment requirements and participant compensation may vary by study site. If you are interested in getting involved, please contact your nearest participating center for further information regarding the enrollment process.

In addition to enrolling subjects with one of the specified demyelinating diseases, we are asking participants to refer affected and unaffected relatives as well as unaffected matched “controls” (such as a childhood friend who grew up in the same area as you or a spouse) for participation in the study.

This is a very exciting opportunity for