CAN INFECTION LEAD TO MENTAL ILLNESS?

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Created in the United States of America

For information regarding this book, contact the publisher:

International Psychotherapy Institute E-Books 301-215-7377 6612 Kennedy Drive Chevy Chase, MD 20815-6504 www.freepsychotherapybooks.org ebooks@theipi.org This book is dedicated to all of you.

Because...You are willing to explore this new area. There are many things in mental disorders we don't understand. The concept that infectious diseases may be involved is only one of them. **Table of Contents**

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Chapter 1: INTRODUCTION

Can infection lead to mental illness?

It's a funny question – and one without a simple answer. In this short book, we will review the data giving the best answer to the question, but here is a short answer.

The discovery of the "germ theory of disease", or the concept that infections were the cause of many illnesses led to dramatic breakthroughs in surgery in the 19th century using aseptic technique at first, and then sterile techniques in surgery. This appreciation of the role of infectious agents in surgery was a clear breakthrough, saving lives. The discovery of antibiotics in the mid-20th century likewise saved countless lives from infections in internal medicine. Appreciation of the role of infections also led to the onset of vaccinations which not only saved lives but also prevented further disability in pediatrics by preventing cases of polio, mumps, measles and rubella. While not all illnesses were prevented, of course, the vast number of infections from these disorders were, leading to healthier children, free of fear of the paralysis of polio, the deafness from measles, or even the discomfort of these viral illnesses.

All along these times, psychiatry continued, studying the mind and the

brain, seemingly impervious to these advances in other medical fields, or a full appreciation of how the body can affect the developing or mature brain, or how infections could also affect the brain. More recently, we have begun to appreciate that infectious agents affect the body, and the brain as well. Likewise, we are understanding that infections can affect the brain not only through its usual function, but also in it development in utero and in childhood in such a way that mental illnesses can result. For at least a decade, evidence is growing that infections, and likely viral infections, can affect the developing brain in such a way that individuals born during a time of the year when these infections are prevalent grow up with a higher risk of schizophrenia. The virus seems to do something to the developing brain making it more likely that the individual will develop schizophrenia.

Likewise, evidence is emerging that many patients with depression have the effects of inflammation in their systems, and this inflammation leads to a higher risk of having a depressive illness. Whether the infection itself affects the brain leading to a mental illness, or whether the inflammation changes the protection of the brain – the "blood brain barrier" – to become more permeable to toxic agents which could then infiltrate and affect the brain is a matter of much debate.

But, it seems that infections and subsequent inflammation affect the brain in a way that make depression, and likely bipolar disorder a bit more common.

Even more astonishing is the emerging data that a parasite-toxoplasma —has an effect on behavior and mental illness. Toxoplasma is a parasite that affects up to one third of the world's population, and comes from contact with cat feces or poorly cooked meat. The parasite can go to muscle cells or the central nervous system. Mothers who have contracted toxoplasmosis are more likely to give birth to children who will later develop schizophrenia. In fact, if you contract the toxoplasmosis parasite as a child you are more likely to develop intermittent explosive disorder. Anger seems to be associated with having the parasite in your system. Even anger directed against yourself, or suicide, occurs more often in those who have contracted toxoplasmosis.

Honest.

So, the simple answer to the question of whether mental illness is an infectious disease is almost certainly sometimes. At this point, the best answer is that less than half the time mental illness is due to an infection or inflammation from an infectious process. But, we really don't understand enough to give a better answer than that.

What we do know is that treatment for mental illnesses has progressed almost agonizingly slowly. Medication treatments for depressive illnesses and for psychosis seems stalled in treatments developed fifteen years ago. Even

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psychotherapies, which made great advances with the use of evidence based research methods have not advanced the field as much as we had hoped. Death rates from suicide remain about the same, despite the fact that death rates from cardiac diseases and cancer are declining.

We seem stuck in our treatments, and in our thoughts about them.

Maybe we need to go back, back to the treatments which quickly advanced other medical specialties in the 19th and 20th centuries. Infectious diseases certainly affect the body, and certainly affect the brain. Of course, many factors affect the brain including genetics, experiences, learning, and trauma. We have gained from appreciating the effects of learning, experiences and trauma, and have developed treatments to help with effects on behavior and the brain. We are beginning to understand the effects of genetics, and what specifically genes do. We hope that this will open up a new array of treatments for us. But, in psychiatry, we have ignored infectious agents as a cause of illness in the body or brain leading to mental illnesses.

Being stuck means that new ways of thought should emerge to help with alternative treatments or understanding of pathology. Exploring infectious agents is one of the ways to do this.

In addition, we are just beginning to understand the role that bacteria have in our lives. Most of the cells we carry around with us are not our own, or "human" cells, but rather bacteria. All of us carry these bacteria, mostly in our gut, but we know little about how they interact with us, or how they affect us. This bacteria baggage, or the "microbiome" can affect the brain in several ways. The brain is, of course, the central control system of the body, with interactions with all parts of the body. To effectively manage the body, the brain needs feedback from all parts of the body. It would be folly to assume that the brain evolved without any feedback from the largest number of cells we carry around – the bacteria in the microbiome. We may well have feedback from these bacteria in the gut via the vagus nerve. In addition, the adrenal axis may provide other feedback. The hormonal or other output of these bacteria may circulate in the blood in a way which can affect us as well. We are just beginning to explore the microbiome and its effects on us.

Recognizing this opens a new chapter in how the body works. We don't know enough to explain it, but we do know enough to wonder about it.

This short book is a beginning exploration into the concept that infectious agents can eventually cause mental illness. Because it is such a controversial, and relatively new area, each thought is referenced to over fifty studies which have been published so you can further explore the data if you are interested, or skeptical. The book is also arranged as a series of bullet points to quickly present data. I find that reading does not keep my attention, so arranging data in bullet points seems to keep my attention focused better. So, each chapter is arranged in this way to make the relatively few points in each chapter.

Each chapter will have a brief summary at the beginning and end of each chapter. If you want to save time, you can simply read this introduction, and then the summary at the end of each chapter. References are provided for the variety of papers discussed if you want to go deeper at any point.

To begin, we will explore in the next chapter the data a brief history of the idea that infections can lead to mental illness. We will then explore data linking the idea that infectious agents can affect the developing brain in such a way that the individual is at more risk to develop schizophrenia. Following this, the link of infectious agents to affective disorders is explored, along with the idea that inflammation may have a role in the production of depressive symptoms. The rate of diagnosis of autism in children has been rapidly growing over the last several decades, and one of the potential explanations for this is that the "microbiome" has been changing with more processed foods, and the increased use of antibiotics in animal feeds. This will be briefly discussed (very briefly, in fact, because this idea has the least amount of empirical support of the various ideas presented in this book). Next, the fascinating story of toxoplasmosis will be presented – presenting data that toxoplasmosis can not only be associated with the development of schizophrenia, but also emotional dysregulation – even enough to cause

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suicide. Finally, we will briefly look at the microbiome, or our body's own collection of bacteria, and how that may affect the development of mental illnesses.

My hope is that an exploration of infectious agents and their role in mental illness will lead to a more full understanding of the pathology behind mental illnesses, but more than that, lead to ideas about treatments for these disorders. For you, I hope that having read about the idea once, even briefly, will keep your ear tuned to the developments which will likely come in the future.

After exploring the topic more, I hope you will ask not "Is mental illness an infectious disease?" but rather, "What new mental health treatments will come from exploring viruses or bacteria in the body?"

So, let's move into the future and explore the role of infectious agents in disease. (Or, as I hope you are now thinking to yourself, let's move back into the 19th or 20th century, and explore the germ theory once more – this time for psychiatry.)

Can infections lead to mental illness? At least sometimes they can.

Chapter 2: HISTORY OF THE CONCEPT

I know that you are skeptical that mental illnesses can be caused by infections. So, to start, let's consider psychiatric illnesses which, although uncommon, have been linked to specific infections in the past.

The idea that infections can lead to certain mental illnesses is not new at all. Infections that affect the body can also affect the brain, and when the brain is hit by an infectious disease, a variety of mental illnesses can result. This observation – that infections can result in a mental illness has been made repeatedly over the last century. For example, Sir William Osler noted an increase in obsessive compulsive disorder symptoms in the early 20th century in patients with a variant of rheumatic fever, caused by the streptococcus. In addition, some observers noted obsessive compulsive disorder symptoms after the flu pandemic of 1917. Streptococcus infections in children (PANDAS) can also lead to obsessive compulsive disorder symptoms.

In addition, it has long been recognized that dementia, or a cognitive decline in adults, can be caused by various infections. The illnesses that have been shown to be caused by infectious illnesses, however are quite rare.

So, while these syndromes are uncommon, they do represent a good starting place for examining the role of infections in mental illness since they are so well known and documented in the history of medicine.

Let's review this evidence:

History Of The Idea That Infections Can Cause Behavioral Problems

- The idea that infections can affect the brain is not new at all.
- Sir William Osler, a physician practicing at the turn of the 20th century at the University of Pennsylvania and Johns Hopkins, noted "a certain perseverativeness of behavior" in patients with Sydenham's chorea, a variant of rheumatic fever (obsessive or compulsive behavior). Those patients who developed this variant of rheumatic fever (an illness caused by the group A streptococcus bacteria) developed symptoms which resembled obsessions or compulsions.)
- Following the flu pandemic of 1917, an increase in obsessive compulsive disorder cases was observed in those who survived the flu. So, it appears that a viral illness can also lead to an increase in obsessive and compulsive symptoms.

PANDAS

- PANDAS are pediatric autoimmune neuropsychiatric disorders which are also associated with streptococcal (group A βhemolytic streptococcal [GABHS]) infections
- The working definition of the syndrome is the presence of

obsessive-compulsive symptoms and/or a tic disorder (that is muscle twitches). The onset is before puberty. The course of the disorder is episodic, with some periods being worse than others. There is an association with group A beta hemolytic streptococcus infections (strep) infections, and also there is an association with neurological abnormalities associated with this syndrome.^[1]

So, strep infections can cause anxiety or obsessive-compulsive symptoms in children as well. If this is suspected clinically, the child is tested for strep, and an antibiotic can be prescribed for treatment of the infection, which helps to treat the psychiatric disorder as well.

Dementia

• There are certain rare types of dementia which can be caused by infections. The most well-known of these is Creutzfeldt-Jakob disease (CJD). This is a rapidly progressive dementia which typically leads to death within a year of its onset. The disease can occur because of a genetic mutation, can occur spontaneously, and much more rarely, can be caused by the transmission of an infectious agent through medical procedures where the victim comes into contact with contaminated blood. This can occur through surgery or giving blood. "Mad Cow Disease", or bovine spongiform encephalopathy, is an example of this type of disease where the infectious agent comes from a diseased cow which is then consumed by the unsuspecting host, leading to the dementing illness. While this is extraordinarily rare,

safeguards remain in place in the United States preventing people from donating blood if they lived in an area where beef cows were not tested for this disorder at that time. So, while rare, it is an example of an infectious agent causing a dementing illness.

- Herpes encephalitis (or a disease where the herpes virus causes a brain infection) can lead to amnestic syndromes where short term memory is severely affected
- HIV disease can lead to dementia as well. This usually occurs in advanced cases where the ill individual has developed associated infectious diseases which then affect the brain, leading to the dementia.

HIV Disease And Suicide Risk^[2]

- After HIV disease was first described, it was clear that those who suffer from HIV disease had an increased suicide risk (RR=3.84 compared to age and sex matched controls)
- However, suicide risk DECREASED after the introduction in 1997 of highly active antiretroviral therapy (HAART) (RR = 2.77). Better treatment led to a decrease in suicide risk. But it is not clear how much of the decrease was due to better treatment of the disease, and how much was due to a decreased cultural stigma associated with the disease, and how much due to a sense of personal hope that suffering from the disease was not a death sentence.

Summary

For over a century, it has been noted that some infections can lead to obsessive compulsive symptoms. While this is not common, it represents a good starting place for our discussion. Infectious illnesses can affect the brain. When this occurs, it has been observed in various places at different times that anxiety disorders, such as obsessive compulsive disorder can be the result.

In addition, dementia, or global cognitive impairment can occur after an infection. This can occur with Kreutzfeldt Jakob disease, so called "mad cow disease", or in a viral encephalitis leading to poor memory. While these types of dementia are not common, they can affect the brain leading to a dementing illness.

While not common, these illnesses give an example of how infections can affect the brain. In general, infections can directly affect the brain through infections or inflammation, or infections can affect the developing brain – causing changes which can then make the brain more likely to be susceptible to a mental illness.

In the next chapter, we will look at evidence linking an increased risk of schizophrenia to infectious agents.

Notes

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Chapter 3: COULD SCHIZOPHRENIA BE CAUSED BY AN INFECTIOUS DISEASE?

For decades, it has been appreciated that the genesis of schizophrenia may well be centered in the changes which affect the developing brain. Demonstrable changes in the brains of those with schizophrenia have been shown by x ray (CT scan and MRI scan) which generally show lower volumes especially in the left temporal areas and frontal lobes. In addition, the overall total brain volume and weight is also reduced in those who suffer from schizophrenia.

It is obvious in looking clinically at those who suffer from schizophrenia that the brain or the "control center" of the person is not working properly. But, the question remains...what may have been at the beginning of this change? What may have caused these brain changes to occur?

In this chapter, we will examine the data suggesting that one of the possibilities which could change the developing brain is a viral infection, in utero or shortly after birth. This idea holds that if a virus affects the developing brain it could lead to brain tissue being laid down differently, or 'pruned' or shaped differently within the brain in such a way that schizophrenia is the result.

Another possibility is that the inflammatory response associated with the infection leads to the change in the developing brain. That is, the infection could set off a cascade of changes which cause the brain to react in a certain way leading to faulty brain development which could lead over time to schizophrenia.

Finally, I will present two studies which shows that the bacteria present (in the microbiome) of those with schizophrenia may be different. That is, those with schizophrenia may have different bacterial make up in their bowels which leads to a different reaction to illness. (This idea is much less cogent, and much more in doubt.)

So, let's begin with the idea that schizophrenia may be the result of an infection in utero or in the post natal period, which affects the developing brain in such a way, that brain development is changed—- leading to schizophrenia.

Schizophrenia: Infections In Utero, And Beyond

- There has long been a suspicion that babies exposed to a viral infection in utero, while the brain is developing, could lead a susceptible person to develop schizophrenia later in life.
- Viral illnesses are seasonal. That is, certain viruses occur at one part of the year, and others occur during other parts of the

year. Some viruses populate the summer months and other viruses occur in winter. Many people notice that they "catch cold" or get a virus in the winter, and wonder if viruses occur only during that season. But, different viruses occur at different times of the year, and winter viruses seem to be more prominent because in the winter, we spend more time indoors – more time close to each other, and it is therefore easier for viruses to spread.

- It has been recognized for some time, that the monthly birth rate of those born with schizophrenia is not random. Rather, there is an increased risk of schizophrenia in those born in late winter. An 11% increase in the risk of developing Schizophrenia is present in those born in February and March. It is thought that viruses during that season play a role in the genesis of the disease.^[3]
- However, it is not clear if the virus at fault attacking the developing brain would be present at the time of birth, or six months earlier when the brain is forming in the developing fetus, or in the months after birth, when brain development continues to be quite rapid.
- Likewise, it is not clear which virus may be at fault.
- But, there are ongoing studies checking increase in IgG antibodies in mothers of patients with Schizophrenia to try to see which viral antibodies may be present to get a better idea of which virus may be implicated.

Many Diseases Also Show Differences In Seasonal Birth Month

- Many diseases are seasonal, with risk varying by birth month. Could different viruses lead to different diseases in the developing body?
- A review of 1,749,400 births of patients cared for at Columbia University hospital (in New York City in the USA) from 1900-2000 was conducted.
- They reviewed 1688 separate diseases, and found that fifty-five were related to birth month (nineteen had been previously reported in the literature). But different diseases had different birth month preponderances (e.g. cardiac diseases were opposite seasons of pulmonary diseases). So, while schizophrenia birth month has a seasonal preponderance – so does over fifty other diseases.^[4]

Viral Infections In Childhood Too?

- So, schizophrenia birth month is not random, and the birth month of many other diseases as well is not random. So, some factor, clearly evident around the time of birth or gestation is playing a role. Viruses are also seasonal. The presence of viruses at different times of the year have been implicated in seasonal differences of birth month for different diseases.
- But, is there more evidence? Could viral illnesses later in childhood also be associated with psychotic illnesses?

- To answer this questions, the Swedish national health registers were reviewed for childhood central nervous system infections for patients aged 0-12.
- In the health registry, the medical data of 1.2 million children were reviewed, and showed 2,435 viral infections, and 6,550 bacterial infections severe enough for the child to be admitted to the hospital.
- Once again, there was a slight increase risk in the risk of psychotic illness with viral central nervous system infections but NOT with bacterial infections affecting the child. While it is not clear which virus was implicated in this slight increased risk, the authors wondered about mumps or cytomegalovirus as being the culprit. ^[5]

No Increased Risk Of Psychosis With Childhood Bacterial Infections

- The prior Swedish study showed no increased risk of psychosis in children who had bacterial infections. Further work showed no increased risk of schizophrenia or psychotic illness associated with childhood bacterial infections.
- So, viral infections but not bacterial infections may well be the agent leading to an increased risk in the development of schizophrenia.

What Could Be Done?

• There does seem to be a small increase in risk of psychosis with

viral Infections. Could this idea lead to prevention of at least some psychotic illnesses?

- For example, if a vaccine for a virus associated with causing an increased risk for psychotic illnesses, could it lead to a "vaccine" for that illness in an attempt to decrease the risk for schizophrenia?
- Some estimate that eliminating the suspected virus in the first 4 to 5 months of pregnancy may decrease the rate of schizophrenia up to 20%.

But, Is It The Virus At Fault, Or The Immune Reaction To The Virus?

- Another competing idea is that it is not the virus itself which is at fault causing injury to the developing brain, but rather the immune response to the infectious agent.
- A study was conducted comparing 43 children with new onset psychosis to 43 children without psychosis.
- 8 of psychotic children (and none of controls) had antibodies ((Ig)G, IgM, or IgA antibodies) to the dopamine-2 receptor (D2R) and NR1 subunit of the *N*-methyl-D-aspartate receptor—Using a cutoff of three standard deviations above the control mean to be significant.^[7]
- This supports the hypothesis that some child psychotic illnesses may be immune-mediated. And, antibodies to the D2 receptor, and to the NMDA complex would make sense in a

disease, where we think that dopamine over activity is important in the genesis of psychotic symptoms.

Could An "Autoimmune Response" Also Be Important In The Genesis Of Schizophrenia?^[8]

- We have seen that a viral illness in utero, at birth, or in early life can be associated with a slight increased risk of schizophrenia. Autoimmune diseases also are associated with an increased risk of schizophrenia as well.
- If so, what could cause this? Benros et al postulate that part of what an infection or inflammation may do to the brain leading to a mental illness is cause increased permeability of the blood brain barrier. The blood brain barrier is a constellation of blood vessels and associated cells which work to block substances coming from the body to the brain to help protect the brain. If this blood brain barrier is breached, then this could open the door for agents which could enter the brain, causing pathology in the brain which can then lead to mental illness. They state. "Autoimmune diseases have been associated with an increased risk of schizophrenia. It has been suggested that brain-reactive autoantibodies are part of the mechanisms behind this association. Furthermore, an increased permeability of the blood-brain barrier has been observed during periods of infection and inflammation."
- In this review, a prior autoimmune infection increased risk of schizophrenia by 29%.

- And, a history of one hospitalization with an infection increased risk for developing schizophrenia by 60%.
- The presence of 3 or more infections and an autoimmune disease leads to a RR of 3.4 (8) (i.e. more than triple the risk of developing schizophrenia.)
- These results linking an infection with the development of schizophrenia remained significant, even after adjusting for substance use and family history of psychiatric disorders in those who developed schizophrenia.
- And, interestingly, hospital contact with infection occurred in nearly 24% of individuals prior to a schizophrenia diagnosis.

Which Virus? Which Immune Response?

- Work is being done on finding the immune molecules in the cerebral spinal fluid (or the fluid which bathes the brain and spinal cord) which may put one at risk for schizophrenia.
- And, levels of these may be higher when someone is at risk for developing schizophrenia than after getting the disease. If true, this could give a marker, or hint of what the troublesome process may be.
- Viral illnesses, or the corresponding immune changes are not the only agent which may be at fault. There is also evidence that schizophrenia or psychotic illness may well correlate with exposure to toxoplasma gondii, a parasite which can

infiltrate the central nervous system.^[9]

Other Ideas About The Immune Response Causing An Increased Risk For Schizophrenia

- Another idea is reflected in the neuroinflammation theory of schizophrenia development.
- Central to this theory is the effect on the brain of microglia, or reactive cells. These are active in the brain, producing proinflammatory cytokines and free radicals. This is toxic to neurons, and causes decreased neurogenesis, and decreased white matter.
- Could schizophrenia be related to microglia activation? This is far from clear, but one idea is that viruses can cause an increase in inflammation, which in turn leads to microglial activation affecting neurons or neurogenesis.^[10]
 - To support this idea, it has been demonstrated that antipsychotics have an anti-inflammatory effect-on microglial activation. Certainly, we do not have a good enough idea about how antipsychotics work, but one idea is that the antipsychotic drugs can be helpful in the treatment of psychosis by dampening this effect of microglia activation, leading to an improvement in the disease itself. [11]

Other Support For The Idea The Neuroinflammation Is Important In The Genesis Of Schizophrenia^[12]

- Pro-inflammatory cytokines are elevated in individuals with schizophrenia compared to controls.
- And, there seems to be elevated microglial cell density in those with schizophrenia – especially in frontal and temporal lobes, thought to be key areas for the genesis of psychotic symptoms.
- Bloomfield et al state, "Microglial activity is elevated in... schizophrenia and...with subclinical symptoms who are at ultra high risk of psychosis and is related to at-risk symptom severity".
- Further, this seems to "suggest that neuroinflammation is linked to the risk of psychosis and related disorders" and ..."is involved in the development of psychotic disorders".

Should Anti-Inflammatory Drugs Be Given To Those Who Have The Disease Or Who Are In The Early Stage Of Development Of The Disease?

- A meta-analysis of anti-inflammatory agents showed an advantage of COX-2 inhibitors only among patients who had a short duration of the disorder. This benefit was mild.
- However, there was no benefit in using anti-inflammatory therapy in patients who have been suffering with schizophrenia chronically. In other words, once the disease was fulminant, anti-inflammatory agents did not seem to help.^[13]

What About Inflammation In The Pre-Natal Period?

- Pre-term children exposed to infection or the inflammation response from these infections are exposed to a greater risk of behavioral disorders.
- One idea holds that it is the inflammatory response itself which leads to the greater risk of behavioral disorders.
- In this inflammatory response, the blood brain barrier (an array of cellular mechanisms which attempt to protect the brain by blocking access to the brain by pathogens) breaks down. With this, there are pro-inflammatory cytokines which cross the compromised blood brain barrier. Also, as part of the process, microglia are activated. With this, there are also neurochemical changes leading to glutamate excitotoxicity. The idea is that these changes cause the brain to react leading to abnormal brain development. This leads to changes in the brain, which could make it more likely to develop schizophrenia in the future.
- In a mouse study, a model of these chronic brain changes were demonstrated, and in addition, these changes led to behavior changes in the mouse into adulthood. This could be a model for how these changes could develop in humans – potentially leading to schizophrenia. ^[14]

Genetic Risk

• The brain, of course, continues to develop throughout childhood

and into adolescence. One of the ways the brain matures is by "pruning" of the neurons in childhood and adolescence. That is, the very large number of synaptic connections are pared down to make management of these connections within the brain a much more reasonable task for the central nervous system to perform.

- One idea is that schizophrenia comes not from the brain being structured, or "put together" abnormally, but rather that the proper "pruning" or organization of synapses does not occur. Here, the proper "pruning" of neurons which could lead to a more efficient neuronal function is missing. In this idea, schizophrenia is the result of the chaotic, or less structured brain.
- The search for genetic influences in schizophrenia is ongoing. In one study, "people with certain variants of C4 genes had unusually high odds of developing schizophrenia, even in the absence of other genetic risks." ...And there is "a link between C4 and synaptic pruning."^[15]
- The study "builds on theories that the over-editing of brain connections in late adolescence might be 'a contributing cause' of schizophrenia."
- The "complement cascade" could affect neuron-microglial interaction, leading to excessive pruning of neurons, leading to schizophrenia. Thus, it may be that infection leads to inflammation which leads to microglial activation within the brain leading to the expression of this gene, leading to an

increased risk of schizophrenia.

Genital Infections?

• Women exposed to genital or reproductive infections surrounding conception (30 days before the last period to 30 days after the last period) have a risk of their children developing schizophrenia FIVE TIMES greater than control (not true in rest of 1^{st} , the 2^{nd} , or 3^{rd} trimester of pregnancy) [16]

Is The Microbiome Different In Those With Schizophrenia?

- This study examined a metagenomic analysis to characterize bacteriophage genomes in oral pharynx (or mouth) of 41 individuals with schizophrenia compared to 33 controls patients.
- In those with schizophrenia, the presence of Lactobacillus phage phiadh, was significantly different in patients with schizophrenia (P < .00037)^[17]
- But, why would this be important in the development of schizophrenia?
- These lactic acid bacteria which were relatively more abundant in schizophrenia, including species of *Lactobacilli* and *Bifidobacterium*, have been shown to modulate chronic inflammation. So, could the different composition of bacteria in those with schizophrenia change the microbiome, as well

as the impact of chronic inflammation in these patients?^[18]

Summary

So, among the questions we are considering is whether schizophrenia could be caused by either a virus, changing the developing brain, or the inflammatory response from the infection. This chapter presents a series of tantalizing clues that infection could be the cause of schizophrenia in at least a substantial minority of the cases. If this is the case, then immunization or anti-viral mechanisms may be considered for treatment of schizophrenia in the future. This could prevent the virus which could cause a faulty structure of the brain, or faulty "pruning" of the neuronal tree within the brain.

If this occurred, then perhaps microglial activation—leading to schizophrenia in the future would not occur.

This data is in its infancy, and while speculative at this point, presents the idea that viruses could be liable for the development of schizophrenia.

The microbiome, or the constellation of bacteria in our bodies, may also be different in those with schizophrenia. The idea of changing this through the use of "pro-biotics" (that is introducing different bacteria into one's system) is another potential therapeutic mechanism which is being considered. Treatment for schizophrenia, let alone ideas on prevention of the illness, has been stuck in the quagmire of current ideas. There is growing evidence that viral infections, or the inflammatory response to those infections may well be important in the genesis of schizophrenia. These novel ideas lead to the hope that other treatment ideas may come which can either more completely treat this devastating illness, or even prevent it from occurring.

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CHAPTER 4: COULD INFECTIONS CAUSE AFFECTIVE DISORDERS?

In this chapter, we will look at data suggesting that like schizophrenia, viral illnesses may be associated with the genesis of bipolar disorder, or at least bipolar disorder with psychotic symptoms.

Then, we will examine the evidence linking either infection, or the inflammatory response which follows infection to the development of depression. Here, not only is there evidence linking inflammation in depression in a subset of patients with the disease, but also treatment ideas are beginning to evolve as the debate surrounding the subject matures.

Could Infections Cause Bipolar Disorder?[19]

In the prior chapter, several studies were reviewed which showed that exposure to viral illness in pregnancy or just after birth is associated with an increased risk of developing schizophrenia. Could the same be true for bipolar disorder?

• If a mother has influenza during gestation of her baby, the risk of developing bipolar disorder in the baby later in life increases almost four fold.

- If this viral infection occurs later in gestation, the risk of developing bipolar disorder was even worse – If the infection occurs in the third trimester, the relative risk is 5.7 (that is if a mother develops influenza in the third trimester, the risk of developing bipolar disorder in the baby is increased 570%)
- This study controlled for maternal age, race, educational level, gestational age at birth, and maternal psychiatric disorders, and still found the increased risk of bipolar disorder if the mother had the influenza virus.

Another Study Examined The Risk Of Developing Bipolar Disorder—With Psychotic Features

We have seen in the prior chapter that the risk of a psychotic illnessthat is -schizophrenia-is increased if the mother is exposed to a viral illness during pregnancy. Could the same be true for another psychotic illness – that is bipolar disorder with psychotic features?

- A study was conducted with a case control design of mothers exposed to influenza (85 patients with bipolar disorder were identified in the study).
- This study, as opposed to the one above found no increased risk for bipolar disorder overall...BUT...
- A five fold increase in bipolar disorder with psychotic features was demonstrated. Could it be that prenatal influenza is a
risk factor for psychosis in bipolar disorder?^[20]

Inflammation And Depression

There is some data linking the inflammatory response to depression, or other psychiatric illnesses.

- Miller and Raison^[21] state that there is "reliable associations of inflammatory markers with psychiatric disorders," and "following administration of inflammatory stimuli" there can be the "induction of psychiatric symptoms." In addition, there seems to be an "association of inflammation-related genes with psychiatric disease."
- There is more data linking depression and the inflammatory response. In fact, depressive symptoms seem to mimic the symptoms someone has when they have the flu virus, and feel ill.
- Benros and colleagues^[22] say that, "Systemic inflammation can induce a 'sickness behavior,' with symptoms of fatigue, reduced appetite, apathy, decreased social interaction, impaired concentration, and sleep disturbances."
- These symptoms are very similar to the vegetative signs of major depression we commonly see.
- Some autoimmune disorders have been linked to depression
- Inflammation is linked to the development of mood disorders

- Typically, it is difficult for some medications or chemicals to reach the brain because of the "blood brain barrier". This is a system comprised of the blood vessels to the brain, with the surrounding glial cells which works to block the influx of materials from the body to the brain. This can make it difficult for many substances to reach the brain and normally helps to protect the brain from toxins.
- However, in depression, this may break down. Benros and colleagues state, "The circulating brain-reactive antibodies and cytokines are particularly likely to reach the brain after compromise of the blood-CNS barriers during periods of stress, infections, and inflammation."
- It is possible that patients with severe depression may have an altered blood brain barrier. That is, inflammatory processes may open up the protective blood brain barrier, leading to inflammatory or toxic effects to affect the brain leading to depressive illnesses.

Let's examine more of the data that link issues in inflammation to the development of a depressive illness.

- A follow up of 3.5 million people born in Denmark, examining data from their national health system was conducted.
- If a person had any history of hospitalization for infection, it increased their risk of having a mood disorder later in life by 62%.

- If the data from everyone who had a mood disorder was examined, 32% of the participants having a mood disorder had a previous hospital contact from an infection. 5% had a previous hospital contact from an autoimmune disease.
- So, how important could this exposure to infections be? "The population-attributable risk associated with hospital contacts for infections accounted for 12% of the mood disorder cases in the present study."
- This risk for developing a mood disorder after an infection did not seem to depend on whether you have a family history of a mood disorder or not. In fact, "persons with a psychiatric family history are not more vulnerable to developing mood disorders than persons without a psychiatric family history" according to Benros, et al.

Is There Any Change Demonstrable In The Blood, Or Cerebral Spinal Fluid From Inflammation In Patients With Depression?

- Patients with depression have an increase in cytokines in their serum and cerebral spinal fluid.
- In fact, the patients who don't seem to respond as well to antidepressant medications have increased inflammatory markers compared to those who respond better to usual antidepressant treatment. (Friedrich, 2014)
- And the baseline plasma concentrations of all studied inflammatory biomarkers are higher in patients who have

been diagnosed with major depressive disorder compared with controls. Four separate biomarkers reach statistical significance looking for this difference. (hsCRP, TNF-alpha, IL6, and MCP-1)

- 12 weeks of escitalopram (an antidepressant) treatment in these patients was helpful, and was associated with reductions in typical depression questionnaires such as the Hamilton Depression Inventory, Beck Depression Inventory, and the Clinical Global Assessment. This improvement was also associated with reduced levels of TNF-alpha, one of the biomarkers of inflammation studied. ^[23]
- Another study also showed elevated levels of cytokines in depression. Cytokines are important parts of the immune response, and they have been shown to be overactive in those with auto-immune diseases.
- A suspected increased risk for depression is postulated in not only those with infection, but also in those who have autoimmune diseases.^[24]
- And in depression–plasma levels of interleukin 6 and Tumor Necrosis Factor are elevated.
- Depression is accompanied by cell-mediated immune activation which, in at least some patients, seems to accompany depressive symptoms.
- Animal models of depression show that a cell-mediated immune response is related to the development of depression-like

behavior.^[25]

This, of course, leads to questions of what antidepressant medications may do in the disease. Antidepressants and mood stabilizers suppress different aspects of cell-mediated and rather specifically target immunity interferon of production. This leads to the auestion how antidepressants may exert their effect. The effect may be broader than the neuroamine hypothesis which hold that circulating levels of norepinephrine or serotonin are decreased, leading to depressive symptoms. Elevating these chemicals then, is thought to improve mood. If the antidepressant medications also have a role in the inflammatory response – this may open up ideas of what the mechanism of action of these medications may be.

Could Treatment With Anti-Inflammatory Drugs Be Considered A Treatment For Depression?

- Kohler et al feel that celecoxib, a non-steroidal anti-inflammatory drug may be associated with some antidepressant response in some patients.
- And, some scant data may show that cytokine inhibitors (that is drugs which reduce the cytokine response to infection) may also have some antidepressant response.
- But, Miller and Raison caution that no psychiatric disorder is an exclusively inflammatory disorder. Only some patients with the psychiatric disorders we have talked about in this book

exhibit changes in their inflammatory response.

- And, Miller and Raison state "data suggest that response to antidepressants may in part be dependent on the induction of inflammatory cytokines".
- So, perhaps giving anti-inflammatory drugs should perhaps be selected only for those patients who seem to have an elevated or abnormal inflammatory response and develop depression. This has not yet been done in research studies on the subject.

Could Treatment For Depression Be "Personalized" For Those Who Show Signs Of Inflammation?

- Patients with major depression who show signs of systemic inflammation have elevated levels of glutamate in regions of the brain linked with motivation.
- Haroon et al.^[26] state "increased inflammation in major depression may lead to increased glutamate in the basal ganglia in association with glial dysfunction".
- Ketamine, and other anti-glutamate treatments are now being investigated as a treatment for depression. So, could anti-glutamate treatments (such as ketamine) be selected for the patients with increased inflammation?

Summary

Again, we have seen a series of tantalizing data suggesting some patients exposed to infections in utero may be more at risk for developing bipolar disorder, or at least in those with bipolar disorder with psychotic symptoms.

Depression is a much more common illness. A series of studies show that in some individuals with depression, there is evidence of an increased risk of inflammatory response in the blood or cerebral spinal fluid. This leads to the question of whether or not inflammation, or the body's response to the inflammatory response may be linked to depression, or even be responsible for the depressive illness in some patients. Indeed, when you have the flu or another viral illness, many of the vegetative signs of depression are present. Could there be a link to the inflammatory response and depressive symptoms? Could those patients with an elevated or altered inflammatory response respond better to either anti-inflammatory agents or agents which target the areas affected by immune response?

This represents another area where the research is evolving, leading to possible new treatments in a disease which affects too many people, and where medication treatment ideas have been rather stagnant.

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CHAPTER 5: AUTISM

The prevalence of the diagnosis of autism in children in the developed world has been rapidly increasing. Some wonder whether this is a true increase, or simply a reflection of more careful diagnosis being now carried out in disabled and troubled children. However, the increase has been so dramatic, so quickly, I believe (just so you know) that at least a large part of the increase in the disorder is real.

What could have changed in the world so rapidly to cause this increase in the number of cases of autism? There are a variety of ideas of changes which could have affected the developing brain leading to an increase in autism.^[27]

There may be an increased use of certain toxins in the developed world leading to changes in the developing brain. But, in addition, diets have changed, leading to more processed food. The food we eat has become progressively different over the last decades. Our food is not different only because of the amount of processed sugars, however. The animals we consume have also been treated with antibiotics, and some wonder if our gut bacteria or our microbiome as a result is different than in decades past. It is becoming evident that the gut communicates with the brain in a variety of ways. The gut may directly communicate with the brain via the vagus nerve. In addition, the gut may influence the rest of the body through the activity of the huge variety of bacteria in the gut and their effects on the body and hence the brain. Any of these changes could be important in the increase in the number of children suffering from autism and autistic spectrum disorders.

These ideas are less in the mainstream than other ideas I have presented in this book, but to have a complete discussion, I am including this chapter for your review. If it causes you to wonder a bit more...than it is worth the few minutes it takes to read this section.

There Are Growing Numbers Of Those With Autism Spectrum Disorders

- In 2000: 1 in 150 eight year olds were diagnosed with an autism spectrum disorder
- In 2006: 1 in 110 children were diagnosed with an autism spectrum disorder
- In 2008: 1 in 88 children were diagnosed with an autism spectrum disorder
- In 2010: 1 in 68 children were diagnosed with an autism spectrum disorder
- In 2012: the rate remained the same. 1 in 68 children were diagnosed with an autism spectrum disorder. ^[28]

- Boys tend to suffer from autism spectrum disorder much more commonly than girls. The male to female ratio is 5:1.
- And, there is a racial difference as well. White children tend to be diagnosed with autism more commonly than black or Hispanic children in the United States^[29]

There Is An Increase In Diagnosis In Autism Diagnoses

- But, is this an increase in diagnostic preferences of clinicians, or does it represent a clear increase in the actual prevalence of the disorder in the community?
- An analysis of data from the National Health Interview Survey may help us.
- This survey showed a 20.9% increase in neurodevelopmental or mental health conditions in children from 2001-2011. (The highest increase occurred in the richest families. Those families who were more than 400% above poverty level had a 28% increase in neurodevelopmental or mental health conditions.).^[30]
- Even though the survey showed an increase in mental health conditions, there was not an increase in all childhood disabilities. In fact, they observed an 11.8% DECREASE in physical disability diagnoses in children. This would tend to support the idea that there is an increase in mental health or neurodevelopmental problems over the last decade.

This Increase In Autism Not Only Leads To Suffering In The Children And Their Families, But An Increased In Cost Of Managing Their Care

- The cost of supporting someone with autism spectrum disorder is high. With an associated intellectual disability, the cost is \$2.4 million per child. If the child does not have an intellectual disability, but still has an autism spectrum disorder, the costs continue to be high-about \$1.4 million.^[31]
- Costs in childhood are special education, and loss of parental productivity; in adulthood, the costs are in residential care, as well as the loss of personal productivity.

Autism Is A Devastating Illness. Can It Be Prevented?

- There are a wide range of ideas of factors which could lead to the increase in autism in the community. Some wonder if an increase of some toxins in environment such as air pollution exposure in 3rd trimester of pregnancy, or exposure to heavy metals may be the cause. Others hypothesize that there is a change in body flora secondary to excessive antibiotic use both in childhood, or changes in animal feed may be a factor in the growth of the illness.
- There is some evidence that prenatal folate may be helpful to prevent autism, though this is not at all clear at this time.^[32]

Could There Be An Increase In Inflammation In Autism?

• In the prior chapter, we examined the data linking an increase in

the inflammatory response leading to some cases of depression. Could there be a link between inflammation and autism?

- Increases in proinflammatory cytokines have been found both in the cerebrospinal fluid of patients with autism spectrum disorder and in the postmortem brain tissue from deceased patients with autism. (Friedrich, 2014)
- How could this happen? One idea is that the overuse of antibiotics, both in treating illnesses in children, as well as the overuse of antibiotics in animal feed may change the gut microbiome. We know that the gut and gut bacteria can influence the brain, and the developing brain. (We will explore this idea in a later chapter.) We can think about certain bacteria and parasites in the gut as helping to dampen the chronic inflammatory response seen normally in children, and that a lack of favorable gut parasites allows proinflammatory cytokines to prevail. The idea is that this could affect the developing brain—leading to more autism in developed countries, or more autism with more development, since the change in diet, or antibiotic use is seen more in developed countries. (Friedrich, 2014)

If Inflammation Is Important In Autism, Is There Any Way To Test The Idea?

• With inflammation, a higher temperature, or fever occurs. So, what would happen if children with autism had their temperature elevated? What would be the result?

- In a small study, 10 children spent alternate days soaking in a hot tub at 102°F (to mimic fever) or at 98°F (control group).
- The children showed improvements when their body temperature was raised to 102°F, compared with the days bathed at 98°F. Benefits were seen particularly in restricted and repetitive behavior as well as social behavior in the children with autism. (Friedrich, 2014)

Could The Inflammatory Response Of Children With Autism Be Changed By Changing Their Gut Organisms?

- This leads to an interesting treatment idea. Could a separate bacteria or organism be introduced into the gut of children with autism? In other words, if the gut bacteria of children suffering from autism is too restrictive leading to an increased risk of the illness, could we introduce other agents which could broaden the microbiota in the gut, or the gut's response to an illness?
- A trial using the *Trichuris suis* ova (TSO), the eggs of a porcine whipworm is now being conducted. *Trichuris suis* ova is safe in humans, does not multiply in the host, is not transmittable by contact, and is cleared from the system spontaneously.
- In a 28-week, double-blind, randomized, crossover study, the patients received TSO for 3 months (2500 eggs every 2 weeks) followed 4 weeks later by placebo treatment for 3 months. After the first 12-week phase of TSO or placebo, the patients entered a 4-week washout before beginning the

second 12-week phase. (13) The trial is not yet completed, and results are pending.

 We will see if this helps to change the gut feedback, or the inflammatory response, leading to changes in children with autism.

Summary

As we have seen in earlier chapters, infection and inflammation have been associated with an increased risk of dementia, schizophrenia, and depression. The rates of autism have been increasing at least for the developed world. The reasons for this are far from clear, but one hypothesis is whether a change in diet, the gut, and the gut microbiome may be responsible for this change.

This idea is far from clear, and the data connected with this is also much less complete than that seen with other disorders discussed in earlier chapters.

But, to be complete, I have included the idea that inflammation, or a change in the gut may be leading to the increase in autism seen over the last twenty years. It represents yet another area where data on inflammation is being examined to see if it may lead to a useful clinical hypothesis. Clear treatment for this disorder continues to be lacking. So many children and adults are suffering from the disorder that new ideas on treatment are desperately needed. While it is far from clear that the data presented here would be important, it will hopefully clear the way to new hypotheses in treatment.

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Chapter 6: TOXOPLASMOSIS

Toxoplasmosis represents the most interesting subject in our search thus far of looking for pathogens in the genesis of mental disorders. It is a parasite, which infects about a third or the world's population. This common parasite, as we will see in this chapter is associated with an increased risk of schizophrenia.

Toxoplasmosis, though, is also linked with a risk of change in behavior. Those with the parasite, which can infiltrate the central nervous system, are more likely to have anger as a problem, and even anger directed against oneself – through suicide and suicidal behavior.

Toxoplasmosis:

- Toxoplasmosis is a parasite, which infects about one third of all humans. (33)
- It is found in cat feces and the parasite can be transmitted by close contact with the cat feces, and it also can be transmitted by consuming poorly cooked meat.
- When ingested, the parasite can go to muscle...and brain.
- Within the brain, it hides within neurons and glial cells. [33]

It Has Long Been Known That Toxoplasmosis Can Be Transmitted To The Baby If The Mother Is Infected

- Other intrauterine infections can be transmitted from the mother to the developing fetus as well.
- However a review of a birth cohort born between 1959 and 1967 showed that maternal exposure to TOXOPLASMOSIS may be a risk factor for schizophrenia in the child when he matures. [34]
- This could be an effect on the developing fetus, or reactivated infection later on in life after the child has been infected with the virus.
- In addition, a retrospective review of those with schizophrenia looked for the presence of toxoplasma antibodies.
- A study of Toxoplasma gondii antibodies in US servicemen with schizophrenia (N=180) was done, and the results were compared to controls.
- There was a positive association between Toxoplasma gondii antibodies and schizophrenia (hazard ratio = 1.24).^[35]

Other Studies On Toxoplasmosis Exposure And Schizophrenia Risk In Adults

• A survey of 45,788 women born in Denmark who delivered a baby from 1992 to 1995 were assessed for Toxoplasma-specific antibodies (IgG AB), or evidence that they had been infected with the toxoplasma parasite.

- This survey showed that for the development of schizophrenia, there was an increased risk of 68% if there was the presence of toxoplasma antibodies (RR=1.68); for schizophrenia spectrum disorders there was a similarly increased rate there was a relative risk of 73% (RR=1.73).^[36]
- In fact, only those with the highest IgG levels had a significantly higher risk of schizophrenia spectrum disorders.
- Reviewing this data and other data linking toxoplasmosis to schizophrenia led Dr. E. Fuller Torrey to wonder if having a cat as a pet in childhood cat was in fact a risk factor for schizophrenia.^[37]

How Could Toxoplasmosis Lead To Schizophrenia Symptoms?

- In rat studies, the toxoplasmosis parasite can invade different central nervous system cells. In fact, dopamine levels are 14% higher in the mice with chronic infections. Higher levels of dopamine is the most common, and most popular neurochemical explanation of the genesis of schizophrenia. [38]
- Haloperidol and like drugs, in fact, are thought to work by blocking dopamine in the brain. In these rat experiments, haloperidol and valproic acid both inhibit toxoplasma growth in vitro. So, could it be that these medications which are commonly used to treat schizophrenia have other effects as well – by inhibiting toxoplasmosis growth in those affected by the parasite?

What Other Illnesses May Be Associated With Toxoplasmosis [39]

- A review of studies showed similar results, that toxoplasmosis may be associated with the development of schizophrenia. Significant odds ratios were found with IgG antibodies to toxoplasmosis with schizophrenia (OR=1.81, p<0.00001).
- IgG antibodies to toxoplasmosis were also found in those with Bipolar Disorder (OR=1.91, p=0.02).
- IgG antibodies to toxoplasmosis were found as well with Obsessive Compulsive Disorder (OR=3.4, p<0.001).
- IgG antibodies to toxoplasmosis were also found in addictions (OR=1.91, p<0.00001).
- However, IgG antibodies were NOT significantly associated with major depression (OR = 1.21, p=0.28).

Does Toxoplasmosis Do Anything Else To The Brain They Inhabit?

- Personality changes in those with toxoplasmosis infection has also been implicated. (Fond et. al., 2013)
- -Could these personality changes or behavior changes lead to behavioral changes enough to cause a psychiatric disorder? —Let's see.

Intermittent Explosive Disorder

- Intermittent Explosive Disorder affects children with sudden anger and outbursts which are difficult to control. Toxoplasmosis has been implicated in the development of schizophrenia, and in personality change. Could it also be implicated in the development of intermittent explosive disorder as well?
- A survey was conducted of 358 patients who were diagnosed with Intermittent Explosive Disorder. (Coccaro et. al., 2016)
- The patients with Intermittent Explosive Disorder were more than twice as likely to have toxoplasmosis as were the control patients in the study.
- But, not only were the patients more likely to have Intermittent Explosive Disorder, but also aggression scores overall were higher in patients with seropositive toxoplasmosis. (Coccaro et. al., 2016)
- Toxoplasma infection was also associated with anger as a problem overall.

Toxoplasma Infection Has Been Associated With Anger And Aggression As A Clinical Problem – What Else?

- Toxoplasma infection has also been studied in its role leading to problems with attention, and directed behavior.
- Latent toxoplasma infection in elders is associated with decreased goal directed behavior, as it seems to "delays

processes of attentional allocation", according to Dr. Beste and colleagues. $[\underline{^{40]}}$

So, How Else May Toxoplasma Affect Behavior

- In studies, toxoplasma infection seems to affect rat behavior.
 - Toxoplasma infection alters the rat's perception of risk being around a cat. Usually, rats have an aversion to cat urine. It is obviously in the rat's interest to avoid being around a cat for the rat's survival. But toxoplasma infection in the rat suppresses this aversion. That is, if a rat is infected with toxoplasma, they lose the aversion to being around cat urine, or being around cats. This would lead to a bad outcome for the rat - they would be much more likely to be killed and eaten by a cat who was around. So, if it is not helpful for the rat, why could it happen? It is not good for the rat – who may well die by being killed and eaten by the cat. But, it would be helpful for the ongoing spread of the toxoplasma parasite. If the rat is infected, and it continues to be around areas where there are cats, it would be eaten, and the parasite would then spread to the cat-influencing the infection cycle, in favor of the survival and spread of the toxoplasma. (Fond et. al., 2013) (That is—it's good for the toxoplasma, but not for the rat. Could the toxoplasma infection of the brain lead to this change in behavior?)
 - In the rat, anti-psychotic drugs are as efficient as anti Toxoplasmosis drugs in preventing these behavioral changes in the rat. The anti-psychotic drugs then help to preserve the

rat from putting itself at risk.[41]

Toxoplasma Causes The Rat To Put Itself At Risk. What About Other Mammals... Including Humans?

- Could it be that a toxoplasma infection in people would put people at risk too? Would people offer themselves up to be victims?
- The presence of toxoplasma infection has been studied in connection with suicide or suicidal behavior in people.

Both The Presence Of Toxoplasma Parasite Infection And The Intensity Of That Infection Is Associated With Suicidal Behavior In Humans

- If a person has been infected with the toxoplasma parasite that is had an antibody to toxoplasma present – this seropositivity of T gondii was associated with a much higher risk of self-directed violence (adjusted odds ratio [OR] = 7.12; 95% CI, 1.66–30.6; P = .008). And, perhaps even more striking, the intensity of the body's reaction to the toxoplasma (the serointensity of T gondii) was also positively associated with a history of nonfatal suicidal selfdirected violence. (adjusted OR = 2.01; 95% CI, 1.09–3.71; P = .03). [42]
 - No similar significant associations were found with cytomegalovirus, and herpes simplex virus type 1 when they were studied in the same research project.

Other Studies On The Presence Of Toxoplasma Infection And Suicide Or Self Directed Violence

- A survey was conducted of 45,788 women born in Denmark who delivered a baby from 1992 to 1995. They were assessed for antibodies to toxoplasmosis – signifying that they had been infected with the parasite (Toxoplasma-specific IgG AB).
 - T gondii-infected mothers had a relative risk of self-directed violence over fifty percent higher (RR= 1.530 compared with mothers who were not infected with toxoplasma. And, the risk of severity of self-injury seemed to increase with increasing IgG antibody level against the toxoplasma parasite. For violent suicide attempts, those who had been exposed to toxoplasmosis had an 80% higher risk of having a violent suicide attempt (RR= 1.810. For completed suicide, the risk was double if you were exposed to toxoplasma (RR= 2.05). A similar association was found for repetition of violence directed against oneself, with a relative risk of 1.54. [43]

Summary

Toxoplasmosis represents perhaps the most intriguing example of an infection leading to psychiatric disorder. Like other pathogens presented in this book, toxoplasmosis is associated with an increased risk of the genesis of schizophrenia in those unlikely enough to be infected with it.

However, more than that, toxoplasmosis infection of the central nervous

system is also associated with changes in behavior. Toxoplasmosis is associated with changes in anger in those infected, and the more severe the infection, the more change seems to be present. Those with intermittent explosive disorder have a higher risk of being infected with toxoplamosis.

But, it is not simply anger – but anger directed against oneself through repetitive self injury, suicide attempts, and actual suicide is also seen in those infected with toxoplasmosis. Studies of the rat show that rats infected with toxoplasmosis are more likely to put themselves at risk – which helps the spread of the toxoplasma. Studies of humans show that humans infected with toxoplasma are also more likely to suffer self harm as well.

One third of the world is infected with the toxoplasma parasite. This parasite, which can infiltrate the central nervous system is associated with changes leading to behavioral change, illnesses such as schizophrenia or intermittent explosive disorder, and even suicide. In the United States, the death rate from cardiac disease and cancer has been declining. However, the death rate from suicide remains stubbornly stable, or may even be increasing a bit over the last decade. No public health intervention has been able to successfully interfere with this increase. The importance of examining this data is that treatment or prevention of toxoplasmosis could be an avenue to explore for better treatment of schizophrenia but also for investigations of suicide prevention.

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Chapter 7: THE MICROBIOME

There is a growing recognition that we live our lives, not on our own, but sharing our bodies with a very large collection of bacteria. In fact, there are more bacterial cells in our body than human cells. Obviously, a population of different species this large inhabiting our own bodies cannot be ignored.

But, what is their effect?

This is not clear, but there is beginning recognition that this large group of bacteria, especially in the bowel, may be important in signaling the brain about stress, in forming the developing brain, and then affecting how the body reacts to stress or anxiety. Researchers have demonstrated some data that seems to indicate that the vagus nerve may well be a pathway for the gut to communicate with the brain, and for the brain, in return to communicate with the gut. In addition, it has long been known that the adrenal glands are important in the stress response, and it is clear that the brain communicates with this system via the hypothalamic-pituitary axis.

Tantalizing bits of data are becoming clearer. If the vagus nerve is cut, there is a decreased risk of developing Parkinson's disease later in life. If a patient takes a medication which blocks stomach acid chronically, the risk of dementia increases by 44%.

This leads to the question – could bodily health or brain health be affected by changing the constellation of bacteria in the gut. In other words, if different, or additional bacteria were introduced into the gut, could this help to treat disease? This is already being done at times in the treatment of clostridium difficile infections in the gut.

At very least, standard, established, groups of scientists are calling for and funding more study into these gut bacteria, their effects, and how it may affect the brain.

Who Are We Really?

The question reflects not an existential examination of our unconscious, but literally a question about what are the cells inside and around our bodies. Are our cells our own, or do we have a variety of other cells for which we are a "host". It turns out that most of "our cells" are not really our cells. Rather, in our bodies, human cells are outnumbered by bacteria. Our bodies consist of about 30 trillion cells, but there are about 40 trillion bacteria which inhabit our bodies, and most of these are concentrated in our gut. [44] This constellation of bacteria surrounding our own cells is called "the microbiome." These bacteria operate in association with our cells – sometimes to help, and sometimes not. There are thousands of different kinds of bacteria, with many different genes, and processes. To ignore the presence

or effect of this great number of bacterial cells, genetic influences, and actions in our own bodies would be folly.

- These bacteria in our bodies act in ways we don't fully understand. Within each bacteria, there are also genetic components operating. In fact, 8 million genes function in these bacteria (more than 30 times the number in our own cells). (ibid)
- There are over 33,000 species of bacteria in the large intestine; 7,947 species on our tongue alone and 4,154 species in our throat.
- In fact, we carry 3 pounds of bacteria around with us all the time.
- There is an increased appreciation of the importance of this microbiome, and the potential role this large number of bacterial influences may have in health and in disease. The former director of the United States National Institute of Mental Health, Thomas Insel, MD, said, "We are, at least from the standpoint of DNA, more microbial than human. That's a phenomenal insight and one that we have to take seriously when we think about human development."
- Reflecting the importance of researching this topic, in September of 2014, four different \$1 million grants were awarded from the United States National Institute of Mental Health to study the effect of the microbiome on behavior.

Gut Bacteria And The Central Nervous System

The largest collection of bacteria in the microbiome system is in the gut. The mouth, tongue, esophagus, stomach, small and large intestine carry tens of thousands of different types of bacteria, with many different roles and functions.

But, what does bacteria in the gut have to do with our emotions, or the brain? There is a growing appreciation that gut bacteria can influence the brain. There is afferent signaling between the brain and the gut. The brain, after all, is the central control system for the body, and to work properly, needs feedback on its various missions. There is feedback from the gut to the brain. Exactly how this occurs remains unclear.

The vagus nerve may provide a highway for this feedback. The vagus nerve has been demonstrated to be in contact with the gut, and is important in the autonomic nervous system. In addition, it has long been known that "stress" can affect the gut, and digestion. Again, while it is clear that emotions can affect digestion, or a "nervous stomach", there is evidence that the gut can supply feedback information back to the brain. One postulated pathway for this feedback may be through the vagus nerve.

This occurs routinely in adults. But, in the developing body, in childhood, the development of the central nervous system is likely also affected by input from the gut as well. This afferent input to the brain may

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well affect the developing brain in the ways that it becomes organized to deal with stress and emotions.

Put simply, Forsythe, et al state, "Gut bacteria influence development of the central nervous systems (CNS) and stress responses".[45]

Dr. Forsythe goes on to say that "There is now robust evidence that gut bacteria influence the enteric nervous system, an effect that may contribute to afferent signaling to the brain."^[46]

What Is Another Way This Signaling To The Brain From The Gut May Take Place?

- While it is not clear if, or exactly how the gut may give feedback to the brain, how much feedback may occur, or how important that feedback may be, there are ideas on how it can occur. The presence of the hypothalamic-pituitary-adrenal access has long been known. That is, the hypothalamus and pituitary glands represent the "master gland" for hormones, and regulation of many processes. Especially for depression and anxiety, the hypothalamus is important in regulation of mood, or the development of depression. In addition, the adrenal gland, which pours out hormones in response to stress is important in the process. There is some evidence that the presence of gut microbiota regulates the set point for hypothalamic-pituitary-adrenal (HPA) axis activity.^[47]
- So, if there is a feedback mechanism, there would be a role for the gut microbiota in the regulation of anxiety, mood, cognition

and pain as part of the overall "stress response". This would lead to an emerging concept of a microbiota-gut-brain axis. This would suggest that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders. This could open up areas for further medication approaches for treatment of anxiety or stress disorders.^[48]

The Role Of "Probiotics" In Treatment Of Psychiatric Disorders

- A psychobiotic is a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from a psychiatric illness. So, if appropriate organisms could be found which help to regulate the stress response, or anxiety, it could represent a novel way to treat symptoms by the ingestion or insertion of alternate or helpful bacteria or organisms.
- The idea would be to introduce an organism that can produce GABA or serotonin to interact with the "brain-gut axis".^[49]

An Already Existing "Probiotic" Treatment For An Illness: Treating Clostridium Difficile Infection Of The Gut

• Clostridium difficile (C. Diff) is a difficult, usually hospital acquired infection of the gut where the suffering individual suffers from severe diarrhea. In the disease, antibiotics typically wipe out much of the gut bacteria, leading to severe diarrhea. Because it is often acquired in the hospital, the offending agent is often resistant to usual antibiotics since

the bacteria lives in an environment (the hospital) where antibiotics are commonly used. So, a very strong antibiotic, with troublesome side effects, vancomycin, is typically used currently to treat C. Diff infections, to try to kill the clostridium difficile bacteria and treat the severe diarrhea.

- In the illness, C. Diff "takes over" the bowel, and because of diarrhea, the already diverse gut cluster of bacteria is washed away with the diarrhea. So, if a more normal balance of gut bacteria could be re-introduced, there may be a better "balance" of bacterial life in the bowel, and therefore be healthier, leading to less diarrhea. So, if bacteria from a healthy bowel could be introduced, then a better balance of gut health could be re-established. "Borrowing" bacteria present in a healthier bowel could reintroduce a more diverse set of bacteria in the bowel, helping to restore health. This idea, of a feces transplant to an ill bowel is not new. The idea is 50 years old that a fecal transplant to restore "normal" bacterial balance would be helpful.
- So, a study was undertaken where patients suffering from C. Diff received a fecal transplant-that is the introduction of feces from another, healthy person. After the first infusion of healthy feces, there was an 81% resolution of symptoms, which increased to an 83% to 94% resolution for recurrent infusions to treat the C Diff. Alternatively, using the usual very strong antibiotic, vancomycin, led to a resolution of symptoms in only 30% of the patients.^[50]
- And by the way, if the feces are frozen, and then taken, that also

works for treating clostridium difficile infection. Using feces which have been frozen, led to 90% of patients seeing improvement with their Clostridium Difficile infection.^[51]

Will Changing Your Gut Change Your Brain? [52]

- This idea is in its infancy. However, to begin to explore the idea, a very small study was conducted. In this study, twelve women were given fermented milk product with probiotics (a compound with active bacterial cultures) twice a day for four weeks.
- Compared to controls, on functional MRI scan of the brain, it "affected activity of brain regions that control central processing of emotion and sensation."
- In mice, there is growing evidence that the gut bacteria affects the mouse brain via the vagus nerve.

Could The Human Vagus Nerve Also Be Important In The Transmission Of Feedback From The Gut To The Brain?

- In the past, a vagotomy or cutting the vagus nerve was commonly performed for peptic ulcer. It was hoped by cutting the vagus nerve, acid production would be decreased, leading to less ulcers. *It was not known then that a bacteria, H.Pylori, was the cause of ulcers.*
- But, still, patients were given surgery where their vagal nerve was severed, and this group represents a cohort which could

be used to see what would happen if the vagus nerve was not able to communicate to or from the gut.

- Denmark, which has a federal health system was selected for study. Patients who received a vagotomy were studied twenty years after the surgery using prospectively collected Danish registry data.^[53]
- The risk of Parkinsons disease was decreased after truncal vagotomy when compared to the general population cohort.
- Svensson et al state this would "suggest that having an intact vagus nerve increases the risk of developing Parkinson's disease. The finding is in accord with a primary pathological process being initiated in the gastrointestinal mucosa, which then uses the vagus as a major entry point into the brain."

Could Reducing Stomach Acid Increase The Risk Of Other Dementing Illnesses?

- Proton pump inhibitors (PPI) are medications often used to decrease stomach acid, and are used to treat ulcers, or the irritation to the esophagus from gastro-esophageal reflux disease.
- A study showed that the use of these PPI inhibitors increased risk of dementia 44% in those who used them daily over years.
- The proton pump inhibitors studied included omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole, and it was shown that the regular use of these drugs

increased the risk of dementia by 44%. The rates of vascular dementia (dementia from stroke) and dementia secondary to Alzheimer's disease were both increased.

- Gomm, vonHolt, Thome, et. al. state that PPI's "have been reported to cross the blood-brain barrier, and so they are able to directly affect the brain", and that was assumed to be the mechanism. In some way, the authors wondered if stomach acid content was altered that it could affect the brain leading to an increase in dementia in the patients who took the stomach acid lowering drugs over time.
- They did not comment on any effect on gut-brain axis. But, using drugs which decrease stomach acid secretion led to a higher risk of dementia.

Global Call For More Information On The Microbiome

- The information presented in this chapter is tantalizing, but far from conclusive. Clearly, the effects of bacteria in our gut could possible play a role in the development of disease, including mental illness. Hopefully, studying this data could lead to the possibility of new or different treatments for many illnesses, including mental illness. This is becoming increasingly recognized.
- In a very rare international signal, scientists simultaneously in the journals *Science*_[55] and *Nature*_[56] called for a worldwide initiative to investigate the microbiome, and its effects on disease.
They called for a unified initiative to harness the Earth's microbiome.

Summary

We are beginning to realize that most of the cells we carry around with us are not "human" cells but rather bacteria which inhabit our bowels, and mouth along with other parts of the body. These bacteria are living organisms and do not only co-exist with us but also exert influences on our health – and likely – on disease. It would be folly to assume that these bacteria can affect only certain parts of our lives or health. Almost certainly, they affect the development of illnesses. We have seen that they can communicate with the brain via the vagus nerve, via the adrenal axis or perhaps through other signaling from the bacteria or through the exertion of their genetic material.

We have seen that cutting the vagus nerve can affect the rate of developing Parkinson's disease later in life.

Could the gut also affect the development of mental illnesses through its connection to the brain as well?

While there is no clear data that the large number of bacteria inhabiting our bodies can lead to mental illness, they almost certainly have a role in our continuing health, and illness. If, or how this occurs remains to be explained. (I hope you will work on this issue.)

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CHAPTER 8: CONCLUSIONS

This book presents a brief review of the effect of infections or infectious agents in our bodies and how they may affect the brain in some way to lead to a mental illness.

It is widely accepted that infections can affect the developing brain, and examples of infections leading to some psychiatric symptoms have been in existence for a century. However, data is developing linking viral infections around the time of birth to an increased risk of schizophrenia or perhaps bipolar disorder. This may be accomplished either through a direct effect of the virus on the developing brain, or through an effect of the inflammatory process on the brain and its development.

Inflammatory changes have long been associated with depression and depressive symptoms. While it is clear that some individuals have inflammatory changes associated with a depressive illness, not all individuals with depression seem to have these changes.

The reasons for the increase in autism and autistic spectrum disorders is far from clear. But, one of the reasons for this increase being investigated is the changes seen in our diet from the overuse of antibiotics and chemicals in our food. Could this change – put rapidly into place in the second half of the 20th century lead to the increase in autism in the population? This idea has perhaps the least amount of data to support it.

However, substantial data links infection with the toxoplasmosis parasite to an increase in risk of developing schizophrenia. Infection with this parasite also is linked to a change in behavior as well. An increase in aggression, as well as an increase in intermittent explosive disorder is demonstrated in those infected with this parasite. Indeed, there is even data linking the parasitic infection to an increased risk of aggression turned against oneself – or suicide. Suicide rates have been remarkably stable over the last decades. While the death rates from heart disease and cancer have been declining, we have been unable to budge the death rates from suicide. Perhaps we need to look in a different direction to find ways to not only treat suicidal behavior, but even to prevent it. Looking at the treatment of toxoplasmosis and its effect on the brain is one such idea.

Finally, in this brief book, we examined the microbiome. It is clear that bacterial cells outnumber human cells in and around our body. To assume that this large number of bacteria has no effect on our health, or disease would be folly. To assume that it has no effect on other illnesses, including mental illnesses would also be folly. We are beginning to understand that the gut, which holds the largest number of bacteria, communicates with the brain in a number of ways. The ways and the amount of this communications is not clear, but it seems clear that this communication with the brain can affect brain function, and brain response. This, of course, also includes the response of the brain leading to mental illnesses as well.

Over the last decades, the treatment of mental disorders has stagnated. Our medications are largely the same type of medications which we have been using for decades, and our psychotherapies have not largely advanced either.

Our patients suffering from mental disorders need, and deserve better treatments. It is clear that surgery advanced dramatically by paying attention to the presence of infections in the second half of the 19th century. It is also clear that internal medicine advanced dramatically by the discovery of antibiotics and its effects on health in the middle of the 20th century. Likewise, pediatrics advanced through the advent of vaccines protecting children from the development of many diseases.

Other fields of medicine advanced by paying attention to the effect of infections on our health, as well as the effect of infections leading to other illnesses. To assume that psychiatry and psychiatric illnesses would be the only group of illnesses where infections would not be an important contributor would be foolish.

The data presented here is only the beginning of the idea that infectious

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disease causes some mental illnesses. A wide array of factors can influence the developing brain, and indeed the mature brain. One of these factors, almost certainly, is infections.

The data presented here suggests that infections can play a role in the development of some psychiatric disorders. The data, so far, suggests that infections play a role in the development of a minority of these disorders. Treating and preventing even this minority of illnesses would indeed be an important accomplishment. However, more important would be an elucidation of how mental illnesses form, develop, and change over the life span. If an understanding of infectious agents and how they can affect the developing brain can lead to further information on treating or preventing mental illness, it would be significant information indeed.

We do not yet have this information.

The purpose of this book is to ask the question: Can infection lead to mental illness?

The answer is sometimes. As more research progresses, and more answers emerge, we will have a better idea of how this occurs, and how often this occurs.

I hope that you will be in the group finding these answers. We clearly do

not know enough about mental disorders and their pathology. We have seen that tantalizing data is beginning to emerge on how infectious agents can affect the developing brain leading to mental illnesses. Inflammation can affect the brain, leading to changes in health, and disease as well. Toxoplasmosis is associated with the development of intermittent explosive disorder in some cases, and even increases the risk of suicide.

Focusing attention on infectious diseases led to vast improvements in surgery, medicine and pediatrics. Likely, it will also occur in psychiatry and mental health.

Go focus the questions...and find the answers.

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This brief book derives from lectures he has given to the psychiatry residents at the University of Pennsylvania over the years, and he is indebted to his students for sharpening both the questions, and the content of this lecture over time.

Dr. Kettl has other books available for a free download at <u>www.freepsychotherapybooks.org</u>. Please explore both *Exploring Elder Psychiatry* and *Sexual Disorders* found at that website.

Also, Dr. Kettl has published a novel, *The President's Secret*, which explores psychotherapy with a victim of sexual abuse – in a fictionalized case. In the book, America's first woman president must face her past of sexual abuse, and how it affects her present decisions, and view of the world. The book hopes to teach psychotherapy in a more entertaining way (you can be the judge if it is indeed more entertaining). The novel is available on Amazon.

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