

## Prions

Have you ever heard of prions? The name prion was coined in 1981 by Dr. Stanley Prusiner to identify the agents that cause a novel type of fatal brain diseases such as Bovine spongiform encephalopathy (BSE or mad cow disease), sheep scrapie and Creutzfeldt-Jakob disease (CJD) of humans.

Mad Cow Disease, is a deadly illness of cattle's central nervous system. Small holes develop in the animals' brains, making them eventually look like big, hole-riddled sponges. Dozens of people in England are thought to have gotten a human form of Mad Cow's Disease, CJD, by eating the meat of infected cattle.

The most interesting thing about these terrible brain diseases is that no one has been able to find for sure the infectious agent—that is, the virus, bacterium, fungus or parasite—that's the cause.

But, an unusual “protein-only” hypothesis has been suggested. It claims that a new kind of infectious agent, a misshapen protein—aka, a prion—is responsible for these brain diseases. It is controversial because it seems almost impossible that something without any genes could cause infections. Proteins contain no genes—rather they are what genes code for, the products of genes.

There are three main features of the protein-only hypothesis:

1. The first is that the active component in prions is an abnormal protein called prion protein (abbreviated PrP).
2. Normal animal cells make a form of PrP that is called cellular PrP (or PrPC as it is scientifically called).
3. The abnormal protein itself transforms the normal host protein to the abnormal form. In other words, PrP converts PrPC into PrP and animals infected with prions make abnormal PrP. In scrapie, abnormal PrP is called PrPSc.

J.S. Griffith first proposed the protein-only theory in 1967 to explain how prions could replicate if they were made of protein but did not contain nucleic acids. He did this 15 years before the discovery of PrPSc and PrPC. Many have called the theory heretical because it describes replication of a pathogenic agent without a nucleic acid genome. Nucleic acids are important because they are what store and transmit genetic information; essentially they are what genes are made of. In fact, the hypothesis is based upon known properties of proteins with the added wrinkle that a protein molecule folded in an abnormal way can alter the folding of another protein molecule and thereby change its biological properties.

Proteins are chains of chemicals called amino acids linked together like beads on a string. There are 20 different amino acids (imagine 20 differently colored beads) and each amino acid has a different chemical behavior. The prion protein has about 250 amino acids.

The amino acid string does not remain linear once it is made, however, because the properties of the different amino acids make the protein fold into a specific shape or conformation. This conformation of a protein determines its function. Different amino acid sequences produce proteins with different conformations and functions. Genes determine the sequence of amino acids in a protein. Changes in the gene (mutations) can

change the amino acid sequence of the protein and alter its conformation and function.

The prion protein (PrP<sup>Sc</sup>) fulfills all the necessary criteria to be the active component of the infectious particle. First, infectious prions isolated from brain tissue contain PrP<sup>Sc</sup>. A process called purification removes molecules that are not part of the prion. The purity of a prion preparation is judged by how much infectivity is present for each gram of protein or nucleic acid. PrP<sup>Sc</sup> is the only protein found in the best-purified preparations. Scientists have looked in these preparations for specific nucleic acids (e.g., virus genes) but have not found one despite searching for more than 30 years. Thus, the only molecule identified in the infectious particle is PrP<sup>Sc</sup>. PrP<sup>Sc</sup> is involved in all known prion diseases. In some cases, PrP<sup>Sc</sup> molecules have a normal sequence but an abnormal conformation. In other cases, a change in the PrP gene sequence (mutation) causes PrP to fold incorrectly.

All mammals appear to have prion protein genes and the gene sequences are similar, but not identical, in related species. Differences in the PrP amino acid sequence play an important role in determining whether prions from one species can infect hosts of another species. This behavior is difficult to explain if prions are not made of prion protein.

PrP<sup>Sc</sup> molecules can bind to PrP<sup>C</sup> molecules in the test tube and convert them to the abnormal (PrP<sup>Sc</sup>) conformation. The sequences of the PrP<sup>Sc</sup> and PrP<sup>C</sup> molecules must be similar for the conversion to work, and thus the behavior of the PrP molecules in the test tube parallels the behavior of prions in nature.

Sometimes prions from different cases of prion disease vary in the way they affect the brain, giving rise to different prion strains. The variation in strain behavior correlates with differences in the conformation of their PrP molecules. Prions isolated from certain new cases of CJD in the United Kingdom that are thought to be caused by BSE prions show unique strain characteristics. Those prions have a PrP conformation that is similar to that of the PrP molecule from BSE prions, but different from that in conventional CJD prions or scrapie prions.

Adding, changing or inactivating PrP genes in normal mice creates genetically engineered mice called transgenic mice. Hamster prions can not infect normal mice but they can infect transgenic mice that have copies of the hamster PrP gene. Infecting the transgenic mice with hamster prions produces new prions that contain hamster PrP<sup>Sc</sup> and can infect hamsters. Conversely, the transgenic mice produce only mouse prions and mouse PrP<sup>Sc</sup> when infected with mouse prions. Those results show that prions prefer to convert PrP molecules that have the same sequence. This is consistent with the protein-only hypothesis but is difficult to explain if prions are not composed of PrP.

The protein-only hypothesis remains controversial because it breaks new conceptual ground. Those who have worked in this field under other paradigms (like the virus or virino hypotheses) are reluctant to accept this new paradigm. Scientists from other fields are more receptive to this hypothesis, however, and thus it has gained broad support. This hypothesis best explains all of the observations about these agents and the diseases they cause. If at some point it fails to do so, the hypothesis will need to be revised or rejected in favor of a better hypothesis. That is the nature of science.

## **Russian Economy**

The economic climate of Russia today has been greatly influenced by its past history and government. The Communist regime that took over Russia in 1917 implemented one of the worst economic programs in world history, and it took many decades to reverse its adverse effects. Today, Russia and its economy continue, in many ways, to lag behind the rest of the modern world as this country struggles both economically and politically with the transition from communism to democratic capitalism. The Communist Regime left many lasting curses: a poor infrastructure, the black market and a culture of corruption, and years of oppression and uncertainty. All of these, to some extent, are still part of the mindset of the people and investors in Russia and continue to cast a shroud over modern day business transactions.

Russia is the largest country in the world, with an area of about 6.5 million square and 145 million inhabitants but is sparsely populated. It is experiencing a population decline of about 0.5% annually. Moscow, Russia's capital, is its largest city with 10.1 million people and is an important economic and business center. Russia has a large number of immigrants, both legal (200,000) and illegal (~1.5 million). Its labor force is skilled and educated, yet unemployment remains high (~8.5%) and millions are still unemployed (women and young mostly) (Wikipedia).

Today Russia is a vestige of its Communist past. At the beginning of the 20<sup>th</sup> century, Russia found herself on the periphery of modern society and in a desperate race to keep up with more industrialized countries. Less than 8% of her population was involved in any type of industrial work (Hanson). The tsarist government at the time was unstable. When Tsar Nicholas II abdicated in March of 1917, Vladimir Lenin and his supporters took control of the government in November 1917 and created the Communist Party (Hanson). This new government immediately nationalized the banking system, railroads and shipping industries. It also tried to stimulate the economy with the New Economic Policy (NEP) which allowed freed grain markets and small-scale capitalism in cities.

After Lenin died in 1924, Josef Stalin gained control of Russia and focused on the economic realm. He believed that the industrialization of the Soviet Union was a century behind the Western world and so was very determined to make up this gap in just a decade's time. Stalin proposed the first of his 'Five-Year Plans' in 1928. Based on a strict output quota system, the Five-Year Plans were aimed at the "swift accumulation of capital resources through the build-up of heavy industry" (Hanson). This included the collectivization of agriculture and the restricted manufacture of consumer goods. During the latter process of collectivization, Stalin continued to export grain to Western Europe to build up currency reserves.

At the time of Stalin's death in 1953, the USSR had become a global superpower but began to crumble as the Communist Party underwent many leadership changes and internal struggles. The Five-Year Plans were eventually deemed a disaster as they were horribly inefficient, left the economy with a poor infrastructure, created an inability of Russian industry to adapt to industrial change, produced pollution, and made corruption and a black market a way of life (Hanson).

When Mikhail Gorbachev came to power in 1985 he realized Russia needed a change and embarked on his three-fold policy of 'Perestroika', or restructuring: glasnost (openness), democratization, and a 'new thinking' in foreign policy (Hanson). Under

Gorbachev Russia gradually moved toward a market economy, but little progress was made. Disagreement among Soviet leaders turned into deadlock and prevented the adoption of a realistic reform program for the Soviet economy as a whole, and led to a severe economic crisis by 1990 and a widespread loss of confidence in Gorbachev's ability to handle economic issues (Colton).

In 1991 Boris Yeltsin was elected president in Russia and led the transition from Communism to democratic capitalism. He initiated a plan, Shock Therapy, to reform the troubled economy. This included: financial stabilization, a limiting of the money supply and cutting government spending; liberalization, the abolition of government control over economic activities; privatization, a transferring of the control of most government-owned enterprises to private individuals and groups; and internationalization, an opening up of the economy to foreign trade and investment (Parrott).

Under Yeltsin, Russia attained a certain degree of financial stabilization through a change in the banking and currency systems. The Central Bank was turned into a two-tiered banking system similar to those of developed capitalist countries. On the first tier was a Central Bank established to regulate the national money supply and lending policies of banks. On the second tier were commercial banks that lent money to businesses and other borrowers (Parrott).

Initially Russia used the Soviet ruble as its currency of exchange, but in 1993 it issued its own new ruble banknote that experienced an immediate decrease in value. In 1992 it was 415 rubles to the dollar; by 1995 it was over 5000. In 1998 there was a redenomination of the ruble, with new banknotes worth 1,000 times the old ones. The ruble's value then became 6.4 rubles per dollar (Parrott).

During the nineties, Russian government revenue declined due to government spending and the corruption created by an overbearing tax system that resulted in many unpaid taxes, tax evasion, and the removal of the financial benefits from taxing goods. This economic climate also leads to a "shadow economy," where this country's production was understated to avoid taxes (Parrott). As a result of this shadow economy and poor auditing practices, true national output of the country is very difficult to measure and official statistics cannot be trusted.

During Yeltsin's presidency and with the collapse of Communism, foreign trade with former communist countries shifted to the west. Export quotas, licenses, and duties were lifted, making trade easier and more accessible. Russia experienced a positive trade balance in the nineties, but the exact balance of trade is hard to gauge due to unrecorded trade flows, smuggling, and illegal trade flows (Parrott).

In general, investors in Russia did not invest their money in the country for the same reason foreign investors did not want to. Many foreign investors were wary of investing in Russia due to the instability and corruption that permeated every aspect of business in Russia. Also, direct foreign investment was limited since foreign investors were excluded from the first phases of privatization. In addition, many sectors still have limits to the amount of foreign investors allowed (Parrott). Foreign investment was, therefore, concentrated in government T-bills and bonds.

As a result of Russia's tumultuous history and forced economic rule, one of the main obstacles that continues to haunt Russia's economic integrity, stability, growth and foreign investment sentiment is corruption. It ranks with imperfection in law enforcement as a negative influence on investment in Russia (MosNews). This year Russia fell in rank

on the Corruption Perception Index (see Figure 2). Ineffectiveness of authorities, lack of reforms, and transparency in government operations all translate into a poor business climate for business and investors (MosNews).

## **Godot**

Though difficult and sometimes baffling to read or (even) view, *Waiting for Godot*, Samuel Beckett's first play, was written originally in French in 1948 as *En attendant Godot*. It premiered at a tiny theater in Paris in 1953. The play's uniqueness compelled the audiences to flock to the theaters for a spectacularly continuous four hundred performances.

*Waiting for Godot* is one of the most important works of our time; revolutionizing theatre in the twentieth century and having a profound influence on generations of succeeding dramatists, including such renowned contemporary playwrights as Harold Pinter and Tom Stoppard. After the appearance of *Waiting for Godot*, theatre was opened to possibilities that playwrights and audiences had never before imagined.

*Waiting for Godot* was a unique outburst on the literary world. It made no claim to have a place in conventional drama; rather, it carried a "fascination" of its own, authenticated by the undercurrent of resentment in accepting the illogical and unreasonable norms of the society.

This play came to be considered an essential example of what Martin Esslin later called "Theatre of the Absurd," a term that Beckett disavowed but which remains a handy description for one of the most important theatre movements of the twentieth century.

"Absurdist Theatre" discards traditional plot, characters, and action to assault its audience with a disorienting experience. Characters often engage in seemingly meaningless dialogue or activities, and, as a result, the audience senses what it is like to live in a universe that doesn't "make sense." Beckett and others who adopted this style felt that this disoriented feeling was a more honest response to the post World War II world than the traditional belief in a rationally ordered universe. *Waiting for Godot* remains the most famous example of this form of drama.

The play opens on a totally surreal note, with a tramp trying to pull off his boot on a lonely road under a leafless tree. There is no horizon, no sign of civilization. For a moment, this scene might even be considered comic. Eventually Vladimir enters and greets Estragon who informs Vladimir that he has spent the night in a ditch where he was beaten. They are very happy to see each other, having been separated for an unspecified amount of time. Estragon has a sore foot and is having trouble taking his boot off.

The two men remember that they are supposed to wait under a tree on a Saturday for a man named Godot. It appears they do not remember the man named Godot very well, but they think he was going to give them an answer. Neither of the two bums knows when Godot will appear, or even if they are at the right place and or even remember the question.

While they are waiting, Estragon falls asleep. Vladimir, suddenly feeling lonely, wakes Estragon. Tired of doing nothing, they begin talking about the tree and the wait, then settle on discussing their sorry condition. They are homeless and penniless, traveling from one place to another.

Estragon gets bored of waiting and suggests that they pass the time by hanging themselves from the tree. They both like the idea but cannot decide who should go first. They are afraid that if one of them dies the other might be left alone. In the end they decide it is safer to wait until Godot arrives. They nibble carrots and turnips for food. Most of the time, they simply wait for Godot.

After a while, Pozzo and Lucky join them. Lucky has a rope tied around his neck and is carrying a stool, a basket, a bag and a greatcoat. Pozzo has Lucky put down the stool and open the basket of food which contains chicken.

Pozzo sits on a stool, relaxes a little and enjoys some chicken and wine. He is abusive to his servant by demanding things and being rude. Eventually Lucky dozes off to sleep, but is awakened by jerks on the rope from his master.

Estragon and Vladimir go to inspect Lucky who intrigues them. They ask why he never puts his bags down. Pozzo will not tell them, so Estragon proceeds to ask if he can have the chicken bones that Pozzo has been throwing away. Pozzo tells him that they technically belong to Lucky but when they ask Lucky if he wants them, he does not reply. So, a hungry Estragon eagerly gnaws the chicken bones thrown on the ground by Pozzo.

Pozzo eventually tells them why Lucky hold the bags the entire time. He thinks it is because Lucky is afraid of being given away. He explains that he and Lucky have been together nearly sixty years. Pozzo laments that he cannot bear it any longer because Lucky is such a burden who is pitiful and old, and he would like to get rid of him soon; on hearing all this, Lucky cries. Estragon tries to comfort him, but is rewarded by a hard kick in the leg from Lucky.

At this point, Pozzo instructs his slave to dance and think and otherwise amuse the tramps. Lucky's entertainment consists of dancing, which is more like an awkward shuffling motion. They then make Lucky think. What follows is a long and jumbled exercise in rambling of religious and political doctrine which always starts ideas but never brings them to completion. Eventually, the master and slave leave the tramps, and Vladimir and Estragon return to their seats and continue waiting for Godot.

A little later, a young boy brings in a message that Godot might see them the next day, at the same hour and at the same place. Both Estragon and Vladimir discuss past events and then decide to depart for the night. Instead, they remain, neither moving from his seat.

The next act begins the next day at the same time in exactly the same fashion: the two tramps meet on the road after a separation. Nothing has changed except that the bare tree has sprouted five or six leaves. Estragon's boots and Lucky's hat are still on the stage. Vladimir is singing a song about a dog that has been beaten until Estragon shows up barefoot.. Estragon reveals that he has been beaten as well, again. Estragon is upset that Vladimir was singing and happy even though he was not there. Both admit that they feel better when alone but convince themselves they are happy when together.

They resume their wait, though Estragon seems to have forgotten the events of the day before. Vladimir tries to remind him of his wounded leg and the unruly slave who kicked him. Estragon's only memory is a vague one about the bone he was given to chew. Bored with waiting, Vladimir spots Lucky's hat, and the tramps begin playing with it. For sometime, they initiate Pozzo and his slave. Still bored, they discuss suicide again, call each other names, and wait for Godot.

After some time, Pozzo and Lucky re- appear. This time, however, Pozzo is blind and being led by Lucky. They are still bound by a rope, though this one is even shorter. Pozzo falls to the ground and cannot get up. In the process of helping him, Estragon and Vladimir also fall to the ground. The scene deteriorates into a burlesque, with characters trying to get up but only managing to become even more entangled. Finally they are able to get up. Pozzo claims never to have met them before and shocks them by claiming that Lucky is mute. He becomes insulted and departs, stumbling away with Lucky.

The sun sets and the moon rises. A messenger boy enters, claiming not to be the same boy as from the day before. His message, however, is the same. Godot will not come today, but will try to come tomorrow.

The two bums decide to leave but cannot go far since they need to wait for Godot. They look at the tree and contemplate hanging themselves. Estragon takes off his belt but it breaks when they pull on it. His trousers fall down. Vladimir says that they will hang themselves tomorrow unless Godot comes to save them. He tells Estragon to put on his trousers. They decide to leave but again do not move. In the end, the eternal hopelessness of life permeates every aspect of both acts of the play.