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Examination session (May or November)

MAY

Year

2013

Diploma Programme subject in which this extended essay is registered: Chemistry  
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Title of the extended essay: How do Prion Proteins change into Prions ? ;  
The development and consequences of Prions in the body.

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The extended essay I am submitting is my own work (apart from guidance allowed by the International Baccalaureate).

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became engrossed in finding more about Dementia, particularly Alzheimer's disease after spending some weeks in an elderly care home, where she was able to help out under supervision and had several conversations with professional care staff, including nurses and doctors. Her research was mostly from research papers with some books, including the IB diploma Biology book. She did not carry out any practical work in the college laboratory.

The topic was viewed by the student more involving chemistry; folding and bonding in protein structure and she opted for a chemistry supervisor; however she was also had access to a biology teacher.

The topic chosen and work attached is a serious attempt to piece current research into these neurodegenerative diseases by focusing on the mechanisms in which prion proteins are converted into Prions. She has worked very much independently to complete this challenging essay title. In speaking to her, she stated that her main difficulty was selecting and condensing the wide number of research material on this poorly understood medical condition. She has made a serious attempt, however her conclusions are inconclusive and has included in her final warrants further research work.

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I have read the final version of the extended essay that will be submitted to the examiner.

To the best of my knowledge, the extended essay is the authentic work of the candidate.

I spent  hours with the candidate discussing the progress of the extended essay.

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**Assessment form (for examiner use only)**

**Achievement level**

<b>Criteria</b>	<b>Examiner 1 maximum</b>	<b>Examiner 2</b>	<b>maximum</b>	<b>Examiner 3</b>
<b>A</b> research question	2	1	2	
<b>B</b> introduction	2	1	2	
<b>C</b> investigation	4	1	4	
<b>D</b> knowledge and understanding	4	1	4	
<b>E</b> reasoned argument	4	0	4	
<b>F</b> analysis and evaluation	4	0	4	
<b>G</b> use of subject language	4	0	4	
<b>H</b> conclusion	2	0	2	
<b>I</b> formal presentation	4	2	4	
<b>J</b> abstract	2	1	2	
<b>K</b> holistic judgment	4	1	4	
<b>Total out of 36</b>		8		

IB Extended Essay; Chemistry

Research Question:

# How Do Prion Proteins Change Into Prions?

Topic: The development and consequences of Prions in the  
body

2012

Student:

Supervisor:

Candidate Number:

School Centre Number:

Exam Session: May 2013

Essay Word Count: 3837 (Excluding titles, footnotes and tables)

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# Abstract

This essay has investigated the effect of Prions on the human body. Prions are derived from naturally occurring prion proteins. Prions, unlike prion proteins, are insoluble and cause neurodegenerative diseases, such as Prion diseases and Alzheimer's disease. This is the consequence of Prions instigating the formation of senile plaques that prevent or reduce the cumulative speed of the electrical signals within the reflex arc. These diseases currently affect a substantial part of society which is predicted to increase significantly within the next fifty years, creating a large social problem because they are fatal. Medical knowledge is currently limited as research has largely focused on reducing the negative behavioural changes, such as increased aggression, to alleviate care problems within Care Homes.

Research consisted of exploring the process of normal protein folding to understand the occasional progression to abnormal situations such as protein misfolding; this type of abnormality results in the formation of abnormal particles, such as Prions. The research also explored protein aggregation in order to ascertain an understanding of the formation of prion diseases. Thus, the prion protein, the Prion and variations of this particle have also been discussed. This essay has also detailed the protein replication process and what results that has on the body. Kuru disease and Alzheimer's disease have also been looked at in detail. Diagrams, tables and graphs have been used in order to further knowledge of the subject. Thus the research has been presented in the following sections: protein folding; protein aggregation and Prions.

This research was conducted in order to establish the mechanism that causes prion proteins to become Prions. The result of this investigation is that scientists have concluded that Prions initiate the transformation of their surrounding prion proteins into Prions but the exact mechanism of this process is undefined.

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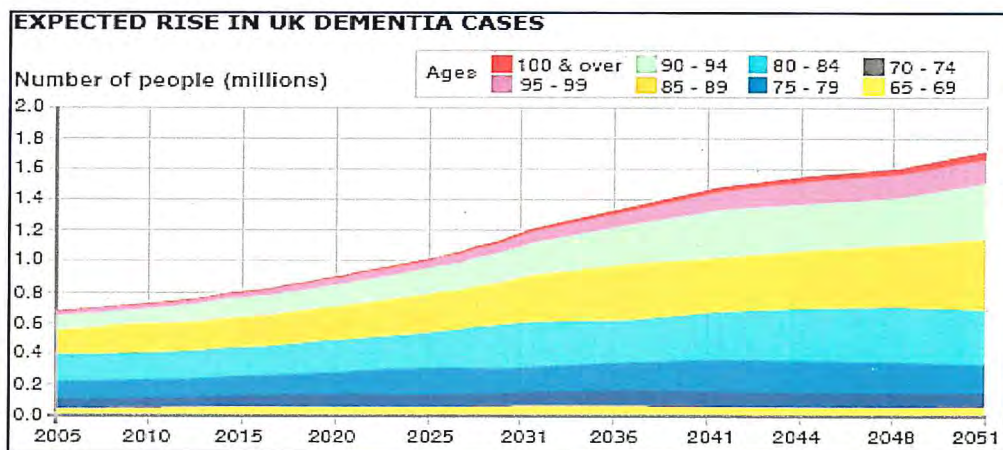


# Introduction

Recent scientific research has suggested that the most common cause of several neurodegenerative diseases, commonly known as Dementia, is the accumulation of protein aggregates, which are toxic to the human body.<sup>1</sup> Dementia is a collective term used to group several neurodegenerative diseases and Alzheimer's disease is one example of these diseases.

As medical knowledge progresses in other fields, such as the prevention of infectious diseases, it has had the result of increasing the life expectancy of the global human population. A study conducted by the Alzheimer's Society has concluded that Alzheimer's disease alone affects 10 percent of those aged over 65 years which increases to 20 percent in those over 70 years old.<sup>2</sup> The research collected showed a direct correlation between old age and the likeliness of being diagnosed with Alzheimer's disease. Thus, it has been predicted that over 1.6 million people will be diagnosed with age-related diseases by 2051, in comparison to 0.7 million in 2010<sup>3</sup>. Figure 1 illustrates the recorded data and the predicted data.

Figure 1: Expected rise in UK dementia cases<sup>4</sup>



The figure above shows the predicted increase in life expectancy with the consequent increase in Dementia, with people aged between 80 to 94 years expected to experience the highest frequency of Dementia.

An increase in cases of Dementia will lead to escalating demands on resources in terms of the cost of medical and other care. Countries with a higher ageing population, such as Britain, will experience the effects of this to a greater extent than developing countries, which have a lower life expectancy.<sup>5</sup> Age-related brain diseases have a varying impact on patients with debilitating effects being experienced between 3 and 20 years after diagnosis.<sup>6</sup>

<sup>1</sup> <http://news.bbc.co.uk/1/hi/health/7846930.stm> [Website] Last accessed 18/12/2012

<sup>2</sup> Ibid.

<sup>3</sup> Ibid.

<sup>4</sup> Ibid.

<sup>5</sup> Ibid.

<sup>6</sup> <http://news.bbc.co.uk/1/hi/health/7846930.stm> [Website] Last accessed 18/12/2012

Current treatment for Alzheimer's disease in the UK prioritises reducing challenging behaviour and pain. In 2009, the National Institute for Health and Clinical Excellence (NICE) declared that drugs such as acetylcholinesterase inhibitors<sup>7</sup> should only be available for moderate staged patients rather than early staged.<sup>8</sup> In order to treat an early staged patient before the Dementia progresses to the moderate stage, thereby requiring more resources and taking into account the wellbeing of the patient, more extensive research is needed to isolate and understand the cause of Dementia, an example of which is Alzheimer's disease.

Alzheimer's disease is caused by the collection of abnormal proteins between the neurons in the brain. The following section will detail the four stages of protein folding along with scientific models to explain how these structures are formed. It aims to present a basic understanding of what is expected during protein folding thereby increasing the understanding of protein misfolding. Misfolding of proteins induces the formation of abnormal proteins, such as neurofibrillary tangles and senile plaques in the brain, which result in Alzheimer's disease.<sup>9</sup>

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<sup>7</sup> Examples of trade names include Aricept, Exelon and Reminyl.

<sup>8</sup> [http://www.alzheimers.org.uk/site/scripts/documents\\_info.php?documentID=122](http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=122) [Website] Last accessed 15/12/2012

<sup>9</sup> <http://news.bbc.co.uk/1/hi/health/7846930.stm> [Website] Last Accessed 20/12/2012



# Protein Folding

Twenty amino acids are required for protein formation. Each amino acid is identified by its unique R group.<sup>10</sup> Different combinations of amino acids have different chemical properties. The extent of the formation of the protein is determined by the bases of the gene that encodes that particular protein.<sup>11</sup>

In order to prepare for a specific function, a protein has to assemble into a unique formation. Proteins are divided according to their shape, in the categories of fibrous or globular.<sup>12</sup> See Appendix 1 and 2 for images of fibrous and globular proteins, respectively. Then they are divided according to their structure. Table 1 summarises the functions of proteins within the human body.

Table 1: Protein functions in the body<sup>13</sup>

Function	Example	Details	Shape
Structural	Collagen	Strengthens bones, tendons and skin; tissues that produce tough collagen fibres between their cells.	Fibrous
Transport	Haemoglobin	Binds to oxygen in the lungs and transports it via the bloodstream to respiring tissues.	Globular
Movement	Myosin	With the protein actin, causes contraction in muscles which result in movement in animals.	Fibrous
Defence	Immunoglobulin	Acts as antibodies. A part of this molecule is able to vary in order to produce many different antibodies.	Globular

<sup>10</sup> <http://click4biology.info/c4b/7/pro7.5.htm> [Website] Last accessed 18/12/2012

<sup>11</sup> [http://www.biology.arizona.edu/biochemistry/problem\\_sets/aa/aa.html](http://www.biology.arizona.edu/biochemistry/problem_sets/aa/aa.html) [Website] Last accessed 14/12/2012

<sup>12</sup> Ibid.

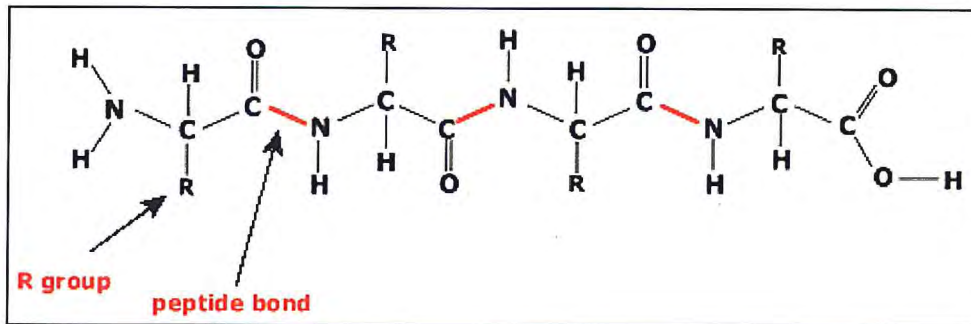
<sup>13</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 68



## Stages of Protein Folding

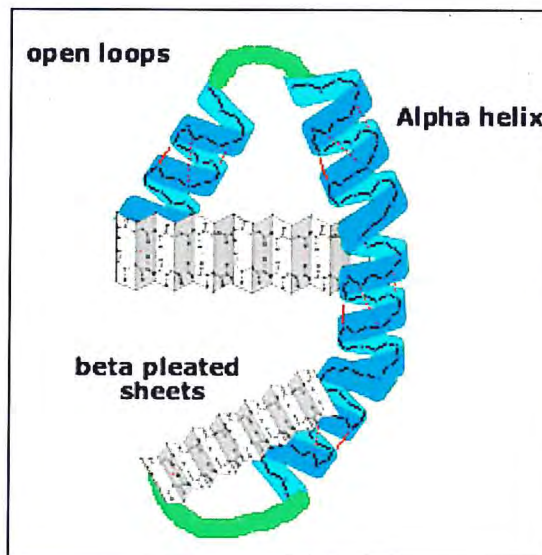
Proteins are further divided according to their structure. The primary structure consists of a chain of amino acids which is called a polypeptide. It is formed of a Nitrogen-Carbon-Carbon (N-C-C) chain with a Hydrogen-Nitrogen-Hydrogen (H-N-H) terminal and a Carbon-Oxygen-Oxygen-Hydrogen (C-O-O-H) terminal; as illustrated in Figure 2.<sup>14</sup>

Figure 2: Primary structured protein<sup>15</sup>



The N-C-C attract to each other due to hydrogen bonding which results in the folding of the polypeptide.<sup>16</sup> This forms the secondary structure. There are three forms of secondary structure in proteins: the  $\alpha$ -helix,  $\beta$ -pleated sheets<sup>17</sup> and open loops. The latter is not formed by a primary structure but serves the purpose of linking  $\alpha$ -helices and  $\beta$ -pleated sheets together.<sup>18</sup> Figure 3 provides an illustration of a secondary structured protein.

Figure 3: Secondary structured protein showing  $\alpha$ -helices (Alpha helixes),  $\beta$ -pleated sheets (Beta pleated sheets) and open loops.<sup>19</sup>



<sup>14</sup> <http://click4biology.info/c4b/7/pro7.5.htm> [Website] Last accessed 15/12/2012

<sup>15</sup> <http://click4biology.info/c4b/7/pro7.5.htm> [Website] Last accessed 18/12/2012

<sup>16</sup> Ibid.

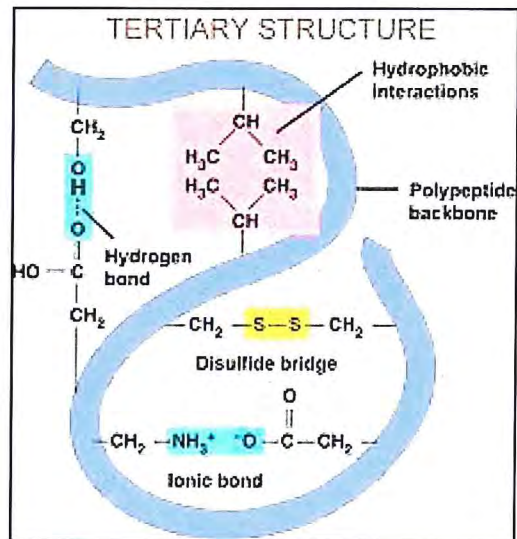
<sup>17</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 68.

<sup>18</sup> Ibid.

<sup>19</sup> Ibid. See Appendix 4 for a further image of a tertiary structure.

The tertiary structure is the “three-dimensional conformation of a polypeptide”.<sup>20,21</sup> It is formed by the polypeptide folding directly after translation.<sup>22</sup> This conformation of the polypeptide is maintained by intramolecular bonds which are located between the amino acids, particularly between R groups. Figure 4 shows the intramolecular bonds that tertiary structures include which are ionic bonds, hydrogen bonds, hydrophobic interactions and disulphide bridges.<sup>23</sup> The increased folding in tertiary structures, in comparison to the secondary structures, is due to the intramolecular bonds that are formed between much closer amino acids in the tertiary structures.

Figure 4: Tertiary structured protein<sup>24</sup>



The final structure of proteins is called the quaternary structure. This is “the linking together of two or more polypeptides to form a single protein”.<sup>25</sup> This means that within a quaternary structure, there are at least two different polypeptides which are joined together to form a single protein. The table below details examples of quaternary structured proteins.

Table 2: The number of polypeptides for specific examples of quaternary structured proteins<sup>26</sup>

Name of Quaternary Structured Protein	Number of Polypeptides
Insulin	2
Collagen	3
Haemoglobin	4

<sup>20</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 67.

<sup>21</sup> <http://click4biology.info/c4b/7/pro7.5.htm> [Website] Last accessed 18/12/2012

<sup>22</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 67.

<sup>23</sup> <http://click4biology.info/c4b/7/pro7.5.htm> [Website] Last accessed 18/12/2012

<sup>24</sup> <http://quizlet.com/5031253/ap-w1-lecture-the-chemistry-of-life-flash-cards/> [Website] Last accessed 14/12/2012

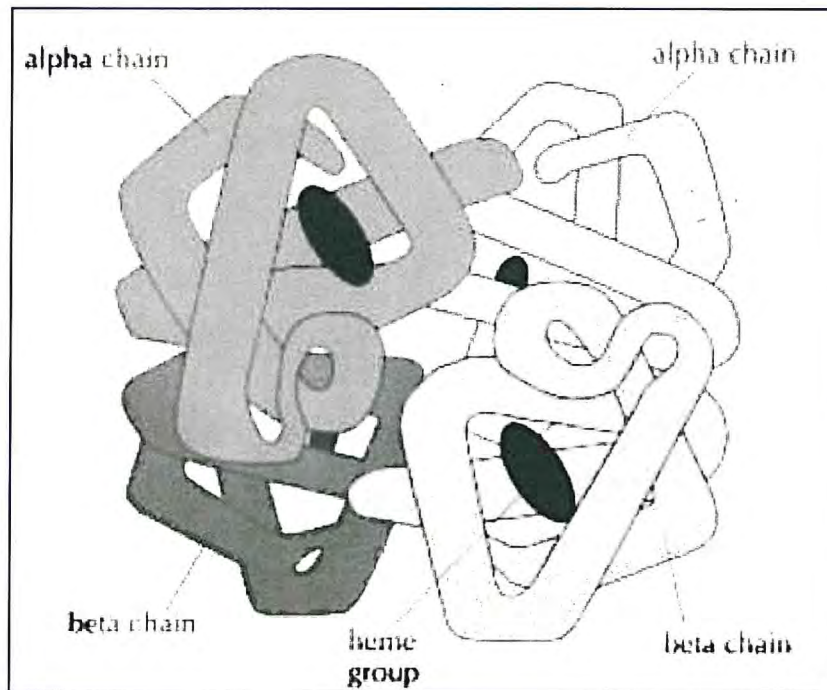
<sup>25</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 67

<sup>26</sup> Ibid.



Uniquely, this structure of protein is able to also contain a non-polypeptide arrangement within the folds of the adjoined polypeptides. This is called a prosthetic group.<sup>27</sup> An example of which is haemoglobin. Each of the four polypeptides is attached to a haeme group. The haeme group is the non-polypeptide structure which is called a prosthetic group within the quaternary protein structure of the haemoglobin. Proteins that contain a prosthetic group, such as haemoglobin, are called conjugated proteins.<sup>28</sup> Figure 5 uses the sausage model to represent the structure of haemoglobin.

Figure 5: A sausage model of the quaternary structured haemoglobin.<sup>29</sup>



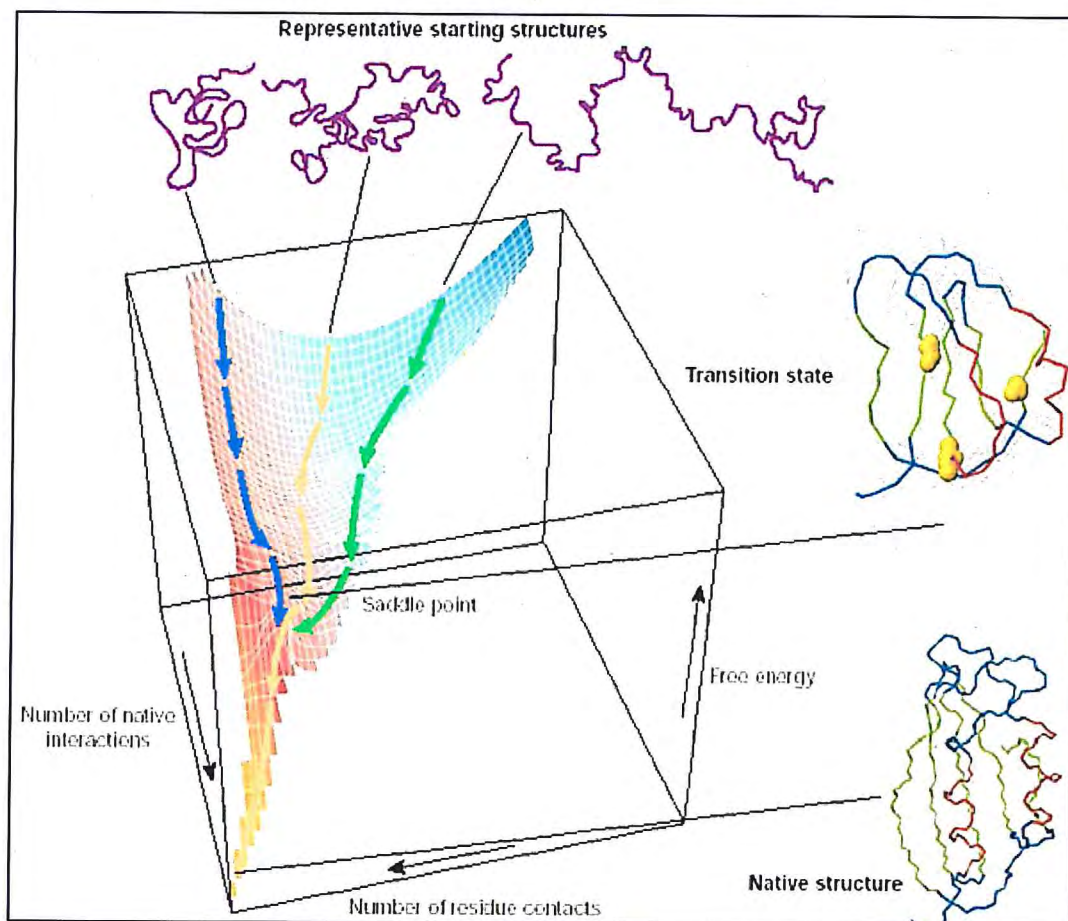
<sup>27</sup> Ibid.

<sup>28</sup> Illott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 67

<sup>29</sup> <http://books.google.co.uk/books?id=xxe6X4wakMUC&pg=PA67&lpg=PA67&dq=sausage+model+of+hemoglobin&source=bl&ots=0V3fO26OG7&sig=9OivoQLpkX9-CuYgXZo0DWPrMMc&hl=en&sa=X&ei=4CftUP6jJ4vZsgbu-oCoBQ&ved=0CDUQ6AEwAA#v=onepage&q&f=true> [Website] Last accessed on 13/09/2012

Anfinsen's thermodynamic folding theory states that proteins fold without a stimulus to achieve the most energy efficient configuration: the native state. This has the minimum amount of energy required to maintain that configuration.<sup>30,31</sup> Protein folding naturally occurs at a fast rate due to the local attraction between the amino acids of the polypeptides. The closer the amino acids are to each other, the stronger the attraction thus there is less energy required to maintain this particular configuration. The increasing strength of local interactions, of the amino acids, has the effect of gradually reducing the conformational area that the protein takes. As seen in Figure 6 below, the conformational area follows a funnel-like shape.

Figure 6: The reducing conformational area of proteins as repeated folding occurs<sup>32</sup>



Scientists have produced several models in order to explain how polypeptides achieve the native state. Scientific models are useful in researching the conformational properties of a protein, the intramolecular interactions and surface properties.<sup>33</sup> Figure 7 provides examples of models.

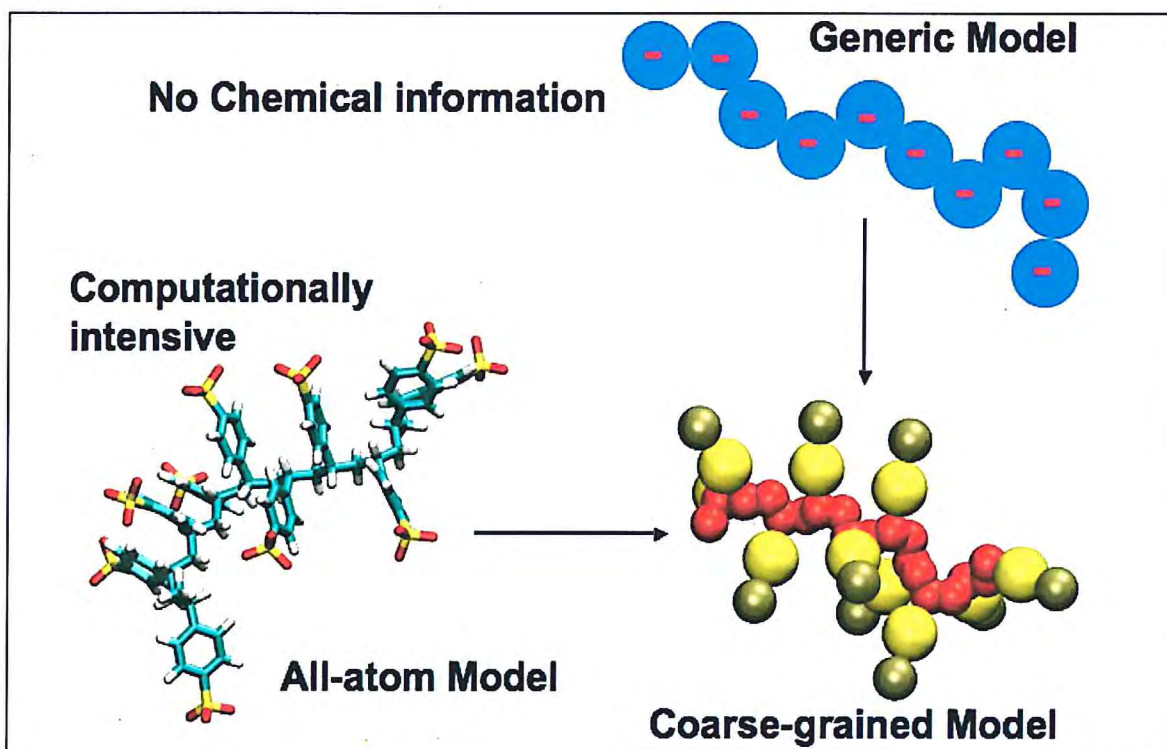
<sup>30</sup> <http://www.enzim.hu/~szia/ownpdf/foldingreview.pdf> [Website] Last accessed on 15/10/2012

<sup>31</sup> For the scheme of Anfinsen's experiment, see Appendix 5

<sup>32</sup> <http://www.nature.com/nature/journal/v426/n6968/full/nature02261.html> [Website] Last accessed on 17/12/2012

<sup>33</sup> <http://yethiraj.chem.wisc.edu/polyelectrolyte> [Website] Last accessed on 17/12/2012

Figure 7: Examples of models used to explain how polypeptides achieve the native state<sup>34</sup>



These models do not contain any chemical information but illustrate, with increasing detail, the suggested structure of the native state. As shown, the particles are not aligned in a straight line; due to local attractions, otherwise known as intermolecular forces.

<sup>34</sup> <http://yethiraj.chem.wisc.edu/polyelectrolyte> [Website] Last accessed on 17/12/2012



# Protein Aggregation

Protein aggregation is the process in which proteins self-assemble into fibrillar aggregates called amyloid fibrils.<sup>35</sup> This process consists of two phases: the nucleation phase and the elongation phase. The nucleation phase is also known as the lag phase and the elongation phase is otherwise known as the growth phase.<sup>36</sup> The figure below shows the entire process of protein aggregation in relation to time.

Figure 8: Protein aggregation against time<sup>37</sup>

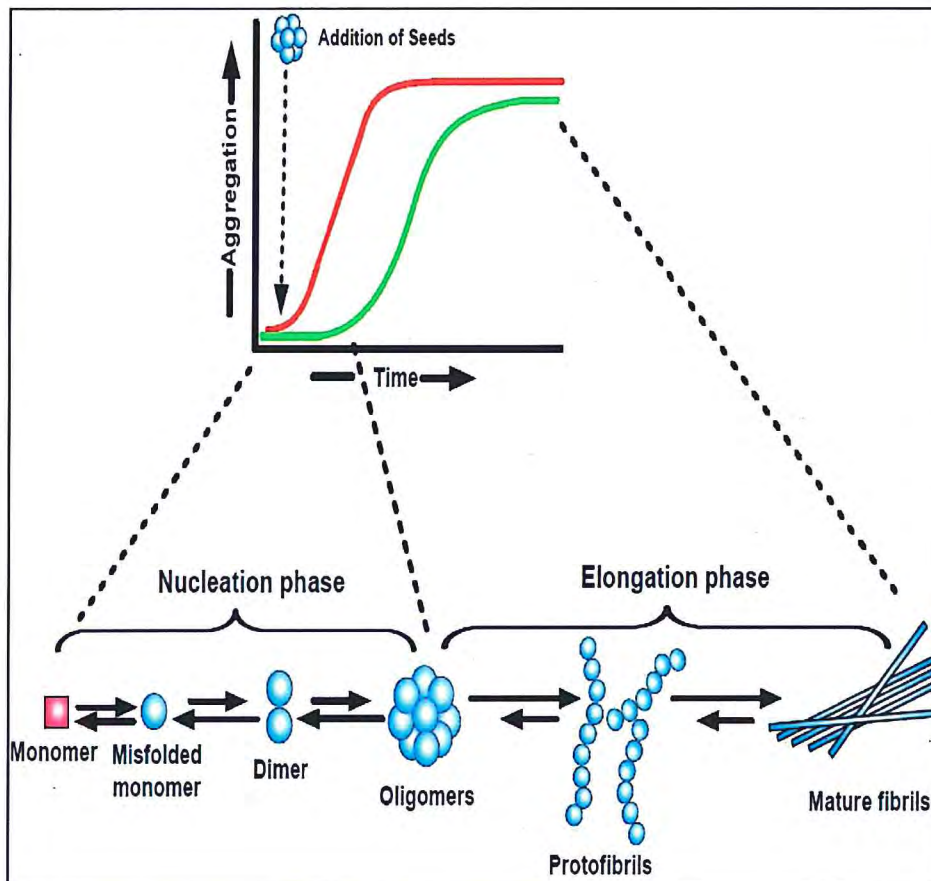


Figure 8 also shows the results of two protein aggregations. The line in red shows the results of this process with a stimulus of the addition of “seeds”<sup>38</sup>. The line in green shows the results of the process occurring naturally. It shows that during the nucleation phase, the monomer protein changes into a misfolded monomer, then into a dimer to form oligomers. Within the elongation phase, the oligomers change into protofibrils which resemble fibrils. Protein aggregation is finished with the production of mature amyloid fibrils.

The nucleation phase is thermodynamically unfavourable which means that it occurs slowly. Figure 8 shows this as where there is a plateau in the line representing the process of protein aggregation.

<sup>35</sup> <http://www.pnas.org/content/early/2012/04/09/1118048109.full.pdf> [Website] Last accessed 25/10/2012

<sup>36</sup> <http://www.molecularneurodegeneration.com/content/4/1/29> [Website] Last accessed 16/12/2012

<sup>37</sup> <http://www.impactaging.com/papers/v3/n8/full/100362.html> [Website] Last accessed 18/12/2012

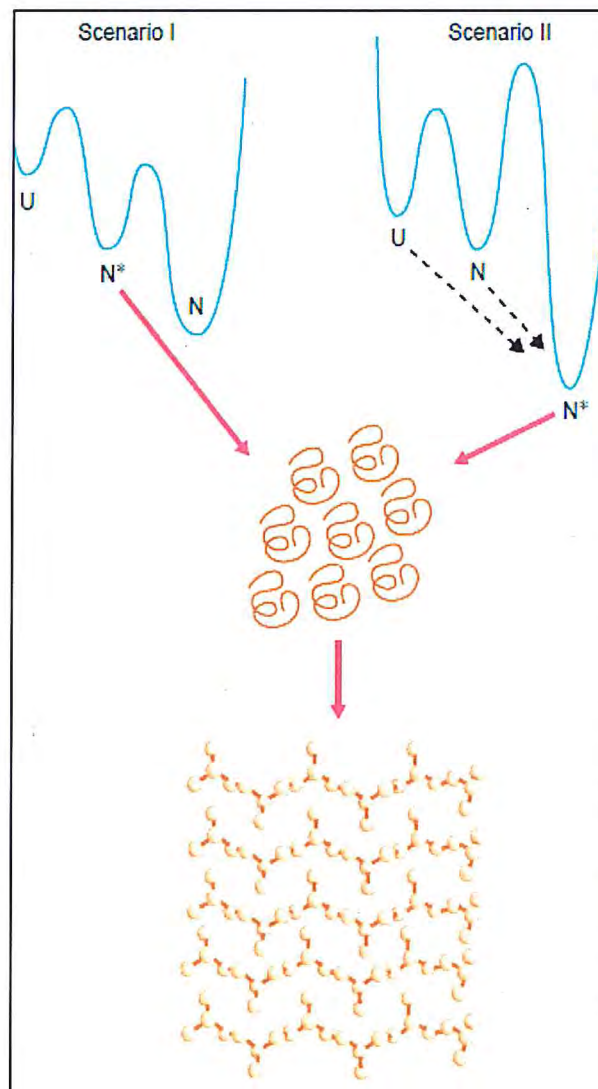
<sup>38</sup> “A small polymer of misfolded prion proteins: no more than 28 molecules”; taken from <http://neuropathology-web.org/chapter5/chapter5ePrions.html> [Website] Last accessed 17/12/2012

Oppositely, the elongation phase is thermodynamically efficient thus advances very quickly. Figure 8 shows this by the significant increase in the rate of protein aggregation.

During the nucleation phase, there are two circumstances where fibrillisation may occur, according to the free energy landscape. Both aim to assemble into the competent state:  $N^*$ . There are two ways that  $N^*$  is created. In Figure 9, "U" is used to abbreviate the unfolded state, "N" for the native state and " $N^*$ " for the competent state. Referring to Figure 9, Scenario I shows that  $N^*$  is formed through partial folding. This shown as the  $N^*$  is presented between the U, the unfolded state, and the N, the native state. Scenario II shows that  $N^*$  may also be formed through either the structural conversion of N, the native state or directly from U, the unfolded state.

After the  $N^*$  structure has been assembled, the amyloid fibrils attract to each other to form protein aggregates. These protein aggregates are intermediates that contain  $\beta$ -pleated sheets. Amyloid fibrils are derived from these intermediates. Thus, amyloid fibrils are highly structured.<sup>39</sup> Figure 9 shows this process.

Figure 9: Showing the two ways in which fibrillisation could occur during the nucleation phase of protein aggregation



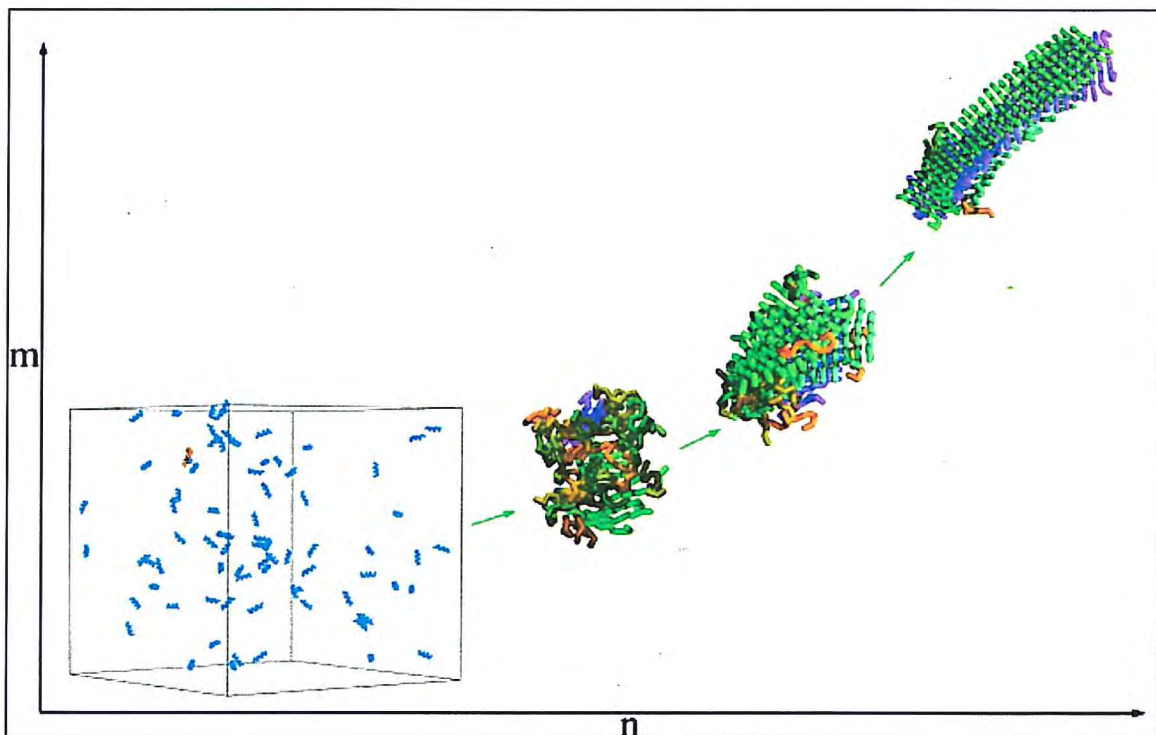
<sup>39</sup> <http://www.molecularneurodegeneration.com/content/4/1/29> [Website] Last accessed on 16/12/2012



The elongation phase also has two ways in which the amyloid fibrils may grow. One prioritises growth in the width which requires an amyloid-competent monomeric conformer. This monomeric conformer deposits on the fibril, adding to its overall area.

The second process is known as the “dock-lock” mechanism. This also requires an amyloid-competent monomeric conformer. However, the monomeric conformer is now absorbed into the amyloid fibril. This part of the process is known as the “dock” section. The “dock” movement has the effect of causing structural change. This results in a configuration that is in accordance with the amyloid fibril structure. This part of the process is called the “lock”.<sup>40</sup> The figure below illustrates this.

Figure 10: Showing the “dock-lock” mechanism of the elongation phase during protein aggregation<sup>41</sup>



This sequence shows the “dock-lock” mechanism of the elongation phase.

<sup>40</sup> <http://www.annualreviews.org/doi/abs/10.1146/annurev-physchem-032210-103526> [Website] Last accessed on 19/12/2012

<sup>41</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2253302/> [Website] Last accessed on 19/12/2012

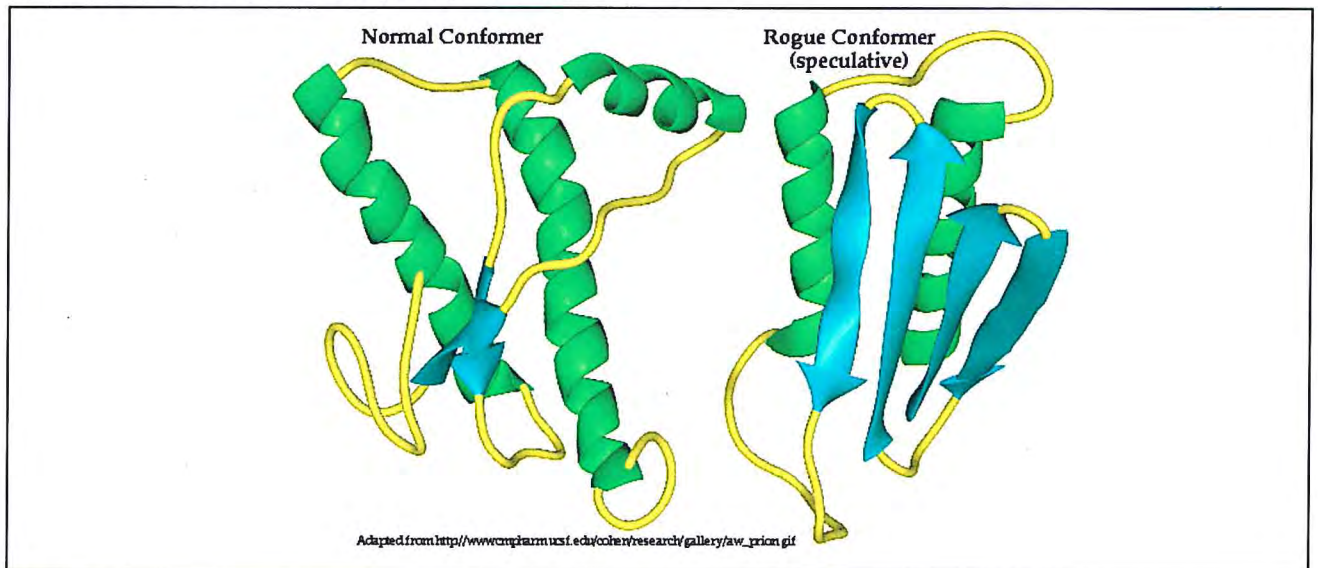


# Prions

The word "Prion" is an abbreviation of Proteinaceous Infectious Particle. Prions derive from prion proteins. A prion protein is a naturally occurring protein that is found most frequently in the brain.<sup>42</sup> It is a protein of 254 amino acids and has the abbreviation of PrP.<sup>43, 44</sup> There are two forms of PrP. The first is referred to as the 'normal form', the prion protein, and is located on the surface of neurons which is called PrP<sup>C</sup>. The second is referred to as the 'abnormal form', the Prion, and binds to PrP<sup>C</sup><sup>45</sup> which is called PrP<sup>SC</sup>.<sup>46, 47, 48, 49</sup> The Prion hypothesis states that "PrP<sup>C</sup> is converted into PrP<sup>SC</sup> by a conformational change".<sup>50</sup> It is PrP<sup>SC</sup>, the Prion, which causes structural change in the surrounding prion proteins.<sup>51, 52</sup> Consequently, the presence of PrP<sup>SC</sup> converts PrP<sup>C</sup>, the prion protein, into another PrP<sup>SC</sup>: creating a positive feedback loop.<sup>53, 54</sup>

The figure below shows the structural differences between the 'normal form', the prion protein, on the left and the 'abnormal form', the Prion which causes disease, on the right.

Figure 11: The structure of the prion protein and the Prion<sup>55</sup>



<sup>42</sup> <http://www.youtube.com/watch?v=w5aAPEYIL9A> [Video source via a website] Last accessed 20/08/2012

<sup>43</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 150

<sup>44</sup> <http://www.news-medical.net/health/What-is-a-Prion.aspx> [Website] Last accessed 16/12/2012

<sup>45</sup> <http://highered.mcgrawhill.com/olcweb/cgi/pluginpop.cgi?it=swf::535::535::/sites/dl/free/0072437316/120088/bio43.swf::How%20Prions%20Arise> [Website] Last accessed on 12/12/2012

<sup>46</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 150

<sup>47</sup> <http://www.youtube.com/watch?v=w5aAPEYIL9A> [Video source via a website] Last accessed 20/08/2012

<sup>48</sup> <http://www.news-medical.net/health/What-is-a-Prion.aspx> [Website] Last accessed 16/12/2012

<sup>49</sup> <http://www.maclester.edu/psychology/whathap/UBNRP/tse10/prionproteins.html> [Website] Last accessed 24/10/2012

<sup>50</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 150

<sup>51</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 150

<sup>52</sup> <http://www.youtube.com/watch?v=w5aAPEYIL9A> [Video source via a website] Last accessed 20/08/2012

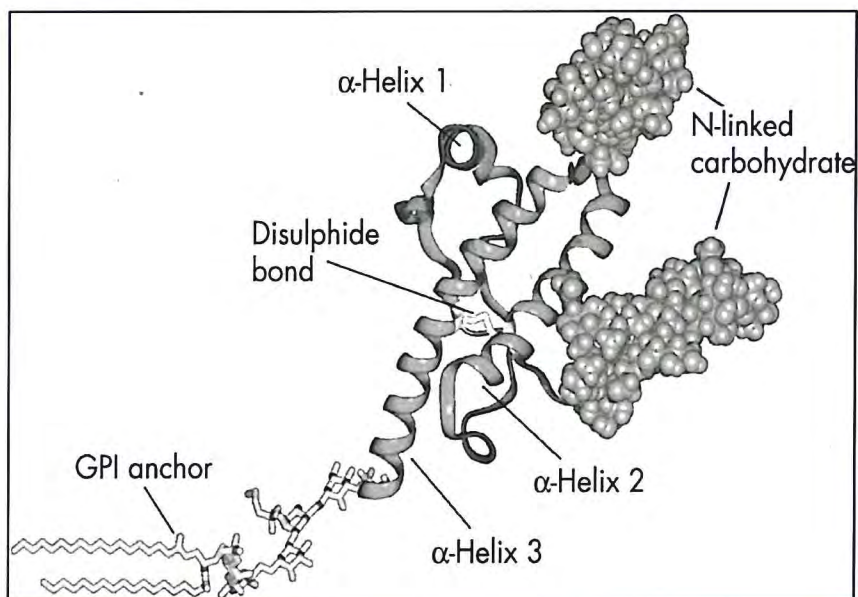
<sup>53</sup> Ibid.

<sup>54</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow. Page 150

<sup>55</sup> [http://www.mad-cow.org/prion\\_structure\\_folder/normal\\_rogue.gif](http://www.mad-cow.org/prion_structure_folder/normal_rogue.gif) [Website] Last accessed 01/12/2012

The Prion, or PrP<sup>SC</sup>, consists of a glycoprotein with two Nitrogen-linked oligosaccharide chains. PrP<sup>SC</sup> molecules congregate on the surface of brain cells, adhering to the phospholipid bi-layer<sup>56</sup> via a C-terminal, glycosyl-phosphatidylinositol (GPI) anchor. The structure of a Prion is shown below.

Figure 12: Structure of a Prion<sup>57</sup>



Prions are found in the body either by being created endogenously, using the host organism for an environment, or it is introduced from the external environment.

Prions change normal prion proteins, PrP<sup>C</sup>, into Prions, PrP<sup>SC</sup>, by infection. This change begins with the production of a polymer of misfolded prion proteins. This polymer is small, consisting of no more than 28 molecules.<sup>58</sup> It is also known as a "seed". It is the "seed" that makes surrounding prion proteins change into Prions. This means that Prions are infectious; relating to their full name<sup>59</sup>. Scientists are still yet to determine the exact mechanism by which Prions change prion proteins into Prions<sup>60</sup> but some scientists have suggested that the Prion, PrP<sup>SC</sup>, activates enzymes which then cause the change to prion proteins.<sup>61</sup>

Figure 13, overleaf, illustrates the known production of Prions from prion proteins.

<sup>56</sup> See Appendix 6 and Appendix 7 for a diagram of a phospholipid bi-layer.

<sup>57</sup> Allott A. (2007). Second Edition. *Biology for the IB Diploma Standard and Higher Level*. Bell and Bain Ltd.: Glasgow.

<sup>58</sup> "A small polymer of misfolded prion proteins: no more than 28 molecules"; taken from <http://neuropathology-web.org/chapter5/chapter5ePrions.html> [Website] Last accessed 17/12/2012

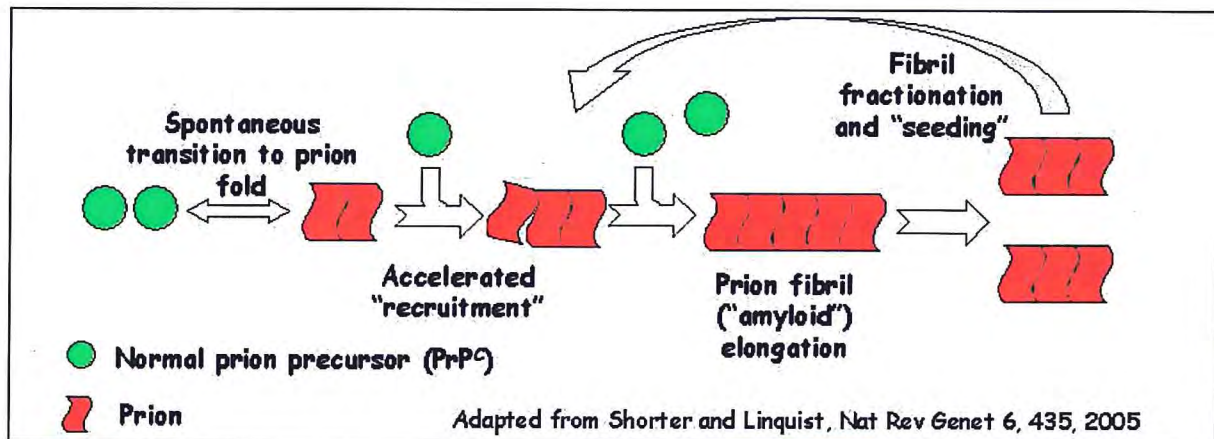
<sup>59</sup> Proteinaceous Infectious Particle

<sup>60</sup> <http://neuropathology-web.org/chapter5/chapter5ePrions.html> [Website] Last accessed 19/12/2012

<sup>61</sup> <http://highered.mcgrawhill.com/olcweb/cgi/pluginpop.cgi?it=swf::535::535::/sites/dl/free/0072437316/120088/bio43.swf::How%20Prions%20Arise> [Website] Last accessed on 12/12/2012



Figure 13: Summary of Prion production, as presented by current medical knowledge<sup>62, 63</sup>



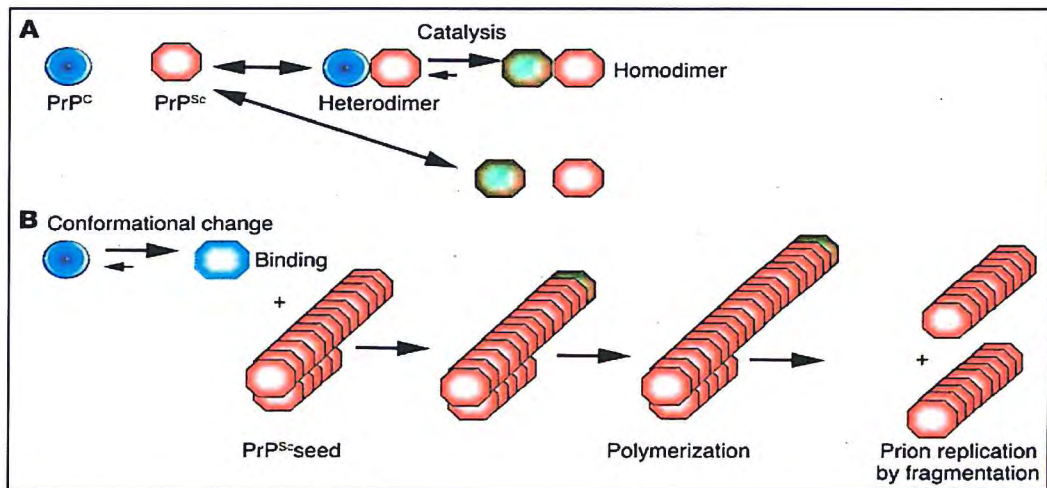
Prions have a unique property in that they are able to postransitionally fold into a protease resistant isoform, PrP<sup>RES</sup>. This has the effect of changing the  $\alpha$ -helix to a  $\beta$ -pleated sheet; subsequently, changing the chemical properties of the particle. Whereas the Prion is highly soluble in water, PrP<sup>RES</sup> aggregates and forms amyloid plaques which are insoluble. This is a very important chemical property change because this is what makes Prions dangerous to humans; Prion diseases are fatal. Prion diseases are discussed further in the following section.

The Heterodimer model, shown in Figure 14 overleaf, suggests that the presence of PrP<sup>RES</sup> provokes the process that changes PrP<sup>C</sup> into other PrP<sup>RES</sup> particles. There is also an alternate model called the non-catalytic nucleated polymerization model which presents the conversion of PrP<sup>C</sup> to PrP<sup>RES</sup> particles as a thermodynamically dependent equilibrium. Direct conversion may occur but only with the condition that a "seed" or an aggregate of PrP<sup>RES</sup> has been added to PrP<sup>C</sup>. Figure 14 illustrates both models.

<sup>62</sup> This figure does not show the exact mechanism.

<sup>63</sup> <http://pandasthumb.org/archives/2005/10/of-prions-and-p.html> [Website] Last accessed 19/12/2012 See Appendix 8 for a similar diagram

Figure 14: The Heterodimer model and the non-catalytic nucleated polymerization model showing the two conversion methods of PrP<sup>C</sup> to PrP<sup>RES 64</sup>



<sup>64</sup> <http://pandasthumb.org/archives/2005/10/of-prions-and-p.html> [Website] Last Accessed 21/12/2012



## Prion Diseases

Prions are the cause of several neurodegenerative diseases. The number of patients diagnosed with these diseases is increasing annually.<sup>65</sup>

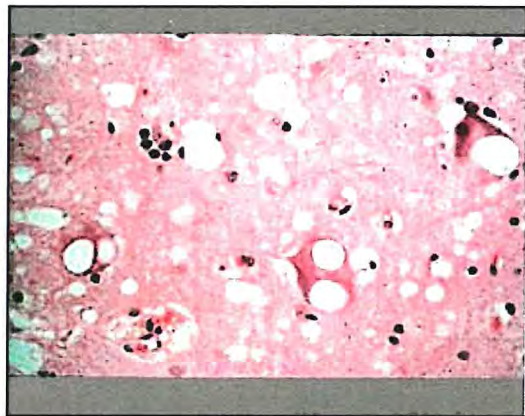
Prions can develop throughout the body but there is a naturally higher frequency of prion proteins contained in the brain so more Prions are produced in this region of the body. Their ability to posttranslationally fold into PrP<sup>RES</sup> means that the Prions are transformed into a state where they are insoluble. This causes the formation of amyloid plaques within the brain that disrupt electrical signals.

Prion diseases often include the aggregation of PrP<sup>RES</sup> within the Central Nervous System (CNS) with a prolonged nucleation, or lag, phase. Most result in the complete malfunction of induced inflammatory responses; which may lead to further ailments in patients.

Prion diseases are also known as Transmissible Spongiform Encephalopathies (TSEs). This is due to the physical changes that occur to the brain during the development of neurodegenerative diseases. Due to neuronal loss, the brain adopts a spongy texture and appearance.

The figure below is a microscopic image of diseased brain tissue. The white circles indicate the large pores that have resulted due to the death of many neurons. This is a main characteristic of neurodegenerative diseases.

Figure 15: A microscopic image of diseased brain tissue<sup>66</sup>



TSEs are able to affect both humans and animals. The following tables show examples of progressive neurodegenerative diseases that affect humans and animals.

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<sup>65</sup> See Figure 1 for dementia case numbers, both documented and predicted.

<sup>66</sup> Modified from

[http://www.google.co.uk/imgres?um=1&hl=en&sa=N&tbo=d&biw=1092&bih=522&tbn=isch&tbnid=mEJQq\\_h0sYCAHM:&imgrefurl=http://learn.genetics.utah.edu/content/begin/dna/prions/kuru.html&docid=11ybwTmTERIKM&imgurl=http://learn.genetics.utah.edu/content/begin/dna/prions/images/BrainSections.jpg&w=361&h=246&ei=6NnpUOX4LoOQ0AWT7oGAAw&zoom=1&iact=hc&vpx=784&vpy=132&dur=25&hovh=185&hovw=272&tx=161&ty=62&sig=106772689580217206263&page=1&tbnh=141&tbnw=208&start=0&ndsp=19&ved=1t:429,r:5,s:0,i:103](http://www.google.co.uk/imgres?um=1&hl=en&sa=N&tbo=d&biw=1092&bih=522&tbn=isch&tbnid=mEJQq_h0sYCAHM:&imgrefurl=http://learn.genetics.utah.edu/content/begin/dna/prions/kuru.html&docid=11ybwTmTERIKM&imgurl=http://learn.genetics.utah.edu/content/begin/dna/prions/images/BrainSections.jpg&w=361&h=246&ei=6NnpUOX4LoOQ0AWT7oGAAw&zoom=1&iact=hc&vpx=784&vpy=132&dur=25&hovh=185&hovw=272&tx=161&ty=62&sig=106772689580217206263&page=1&tbnh=141&tbnw=208&start=0&ndsp=19&ved=1t:429,r:5,s:0,i:103) [Website] Last Accessed 20/12/2012

Table 3: Examples of neurodegenerative diseases that affect humans

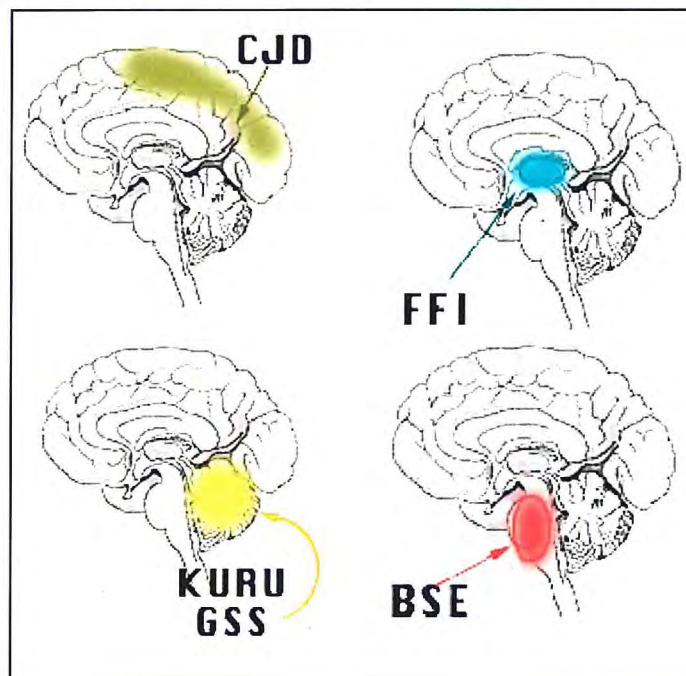
Organism	Name of Neurodegenerative Disease
Human	Creutzfeldt-Jakob disease (CJD)
Human	New Variant CJD (nvCJD)
Human	Kuru
Human	Gerstmann-Straussler-Scheinker syndrome (GSS)
Human	Fatal Familial Insomnia (FFI)

Table 4: Examples of neurodegenerative diseases that affect animals

Organism	Name of Neurodegenerative Disease
Animal	Bovine Spongiform Encephalopathy (BSE)
Animal	Chronic Wasting disease (CWD)
Animal	Scrapie
Animal	Transmissible Mink Encephalopathy
Animal	Feline Spongiform Encephalopathy
Animal	Exotic Ungulate Spongiform Encephalopathy

The figure below shows the regions of the brain that are affected by some of the examples discussed above in Table 3 and Table 4.

Figure 16: Brains affected by different neurodegenerative diseases<sup>67, 68</sup>



The following sections discuss the neurodegenerative diseases, Kuru disease and Alzheimer's disease.

<sup>67</sup> Shaded regions indicate diseased areas of the brain.

<sup>68</sup> <http://www.nobelprize.org/> [Website] Last Accessed 18/12/2012



## Kuru Disease

Kuru is an extremely rare and fatal brain disease. Most case studies are within the period of between 1950 and 1970. This was a time when there was a significant increase in diagnosed cases among the Fore tribesmen who live in the highlands of Papua New Guinea. Epidemic levels were reached as a result of the cultural practice of cannibalism amongst the tribe which was a ritual performed after a death. It was the family of the deceased who had the role of preparing and consuming the human remains. The men ate the majority of the remains whereas the women and children tended to eat tissues only from the Central Nervous System (CNS).<sup>69</sup>

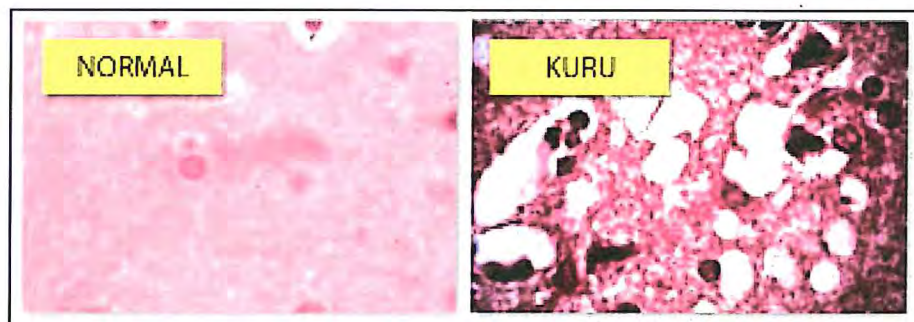
This significantly increased the number of cases diagnosed as infected brain tissue is infectious. Infection may have also resulted from not only the consumption of tissue but contact with open wounds from the infected person. Governmental action of discouraging cannibalism achieved a considerable decline in diagnosed cases. Kuru disease today has now nearly disappeared.<sup>70</sup>

Kuru disease has the characteristic long nucleation, or lag, phase of TSEs. Subsequently, it may have been several years before an infected person would have shown symptoms.<sup>71</sup> Kuru disease was shown to most severely affect the part of the brain called the cerebellum<sup>72</sup>. Resultantly, the decreased lack of control regarding motor coordination was among the first symptoms in diagnosed cases.<sup>73</sup>

In contrast to many TSEs, the symptoms of dementia were mostly absent in cases. However, sudden mood changes and the inability to stand or eat were common. Most of the people diagnosed with Kuru disease lived between 6 to 12 months after symptoms were first shown.<sup>74</sup>

Figure 17 shows the difference in healthy tissue and that of diseased Kuru tissue. The white areas of the image show the diseased tissue.

Figure 17: Healthy tissue compared to Kuru infected tissue<sup>75</sup>



<sup>69</sup> <http://www.ninds.nih.gov/disorders/kuru/kuru.htm> [Website] Last Accessed 18/12/2012

<sup>70</sup> Ibid.

<sup>71</sup> Ibid.

<sup>72</sup> See Appendix 9 for diagram of brain showing cerebellum.

<sup>73</sup> <http://www.ninds.nih.gov/disorders/kuru/kuru.htm> [Website] Last Accessed 18/12/2012

<sup>74</sup> Ibid.

<sup>75</sup> Modified from

[http://www.google.co.uk/imgres?um=1&hl=en&sa=N&tbo=d&biw=1092&bih=522&tbm=isch&tbnid=mEJQg\\_h0sYCAHM:&imgrefurl=http://learn.genetics.utah.edu/content/begin/dna/prions/kuru.html&docid=11ybwmTwTERIKM&imgurl=http://learn.genetics.utah.edu/content/begin/dna/prions/images/BrainSections.jpg&w=361&h=246&ei=6NnpUOX4LoOQ0AWT7oGAAw&zoom=1&iact=hc&vpx=784&vpy=132&dur=25&hovh=185&hovw=272&tx=161&ty=62&sig=106772689580217206263&page=1&tbnh=141&tbnw=208&start=0&ndsp=19&ved=1t:429,r:5,s:0,i:103](http://www.google.co.uk/imgres?um=1&hl=en&sa=N&tbo=d&biw=1092&bih=522&tbm=isch&tbnid=mEJQg_h0sYCAHM:&imgrefurl=http://learn.genetics.utah.edu/content/begin/dna/prions/kuru.html&docid=11ybwmTwTERIKM&imgurl=http://learn.genetics.utah.edu/content/begin/dna/prions/images/BrainSections.jpg&w=361&h=246&ei=6NnpUOX4LoOQ0AWT7oGAAw&zoom=1&iact=hc&vpx=784&vpy=132&dur=25&hovh=185&hovw=272&tx=161&ty=62&sig=106772689580217206263&page=1&tbnh=141&tbnw=208&start=0&ndsp=19&ved=1t:429,r:5,s:0,i:103) [Website] Last Accessed 20/12/2012



## Alzheimer's Disease

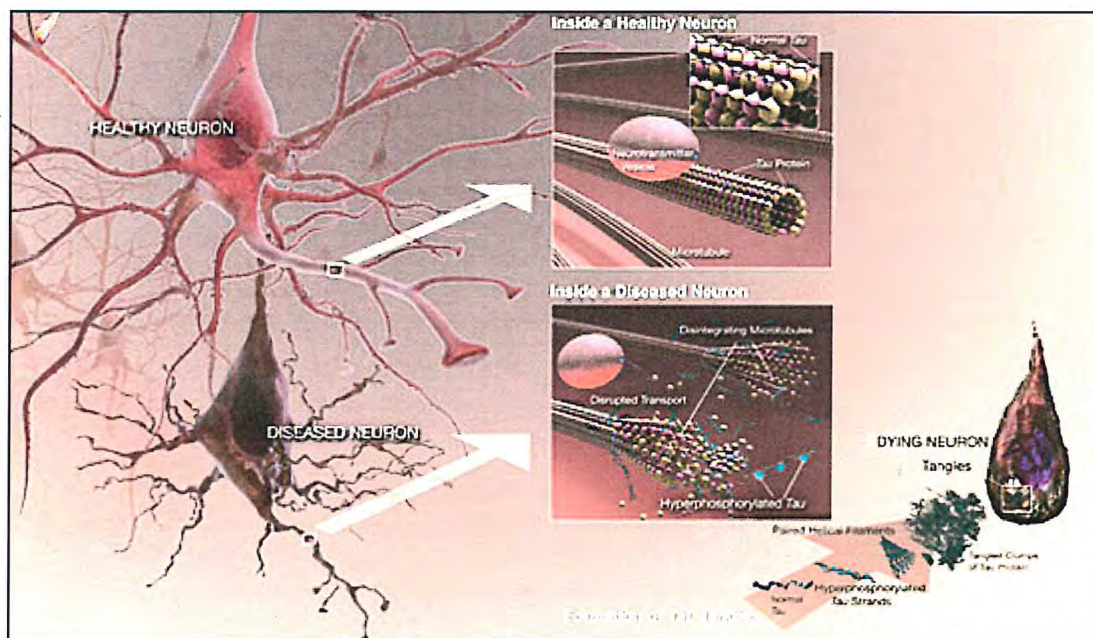
Alzheimer's disease is a progressive neurodegenerative disease that mainly affects elderly people.<sup>76</sup> It is named after its discoverer Alois Alzheimer, who first identified the condition more than a century ago; after studying a patient who had short term memory loss. It was during the autopsy that Alzheimer discovered that within their cerebral cortex,<sup>77,78</sup> there were abnormal bundles of nerves which he called neurofibrillary tangles and cellular debris surrounding these nerves, called senile plaques.<sup>79</sup>

Alzheimer's disease causes the increase in the number of neurofibrillary tangles within neurons. Between each neuron, there is a presence of senile plaques also known as  $\beta$ -amyloid plaques.<sup>80,81</sup>

Neurodegenerative diseases attack the neurons in the body and gradually reduce the entire number of healthy neurons. Neurons are located in CNS tissue and transmit electrical signals from the brain to the rest of the body. This flow of signals enables us to function on a daily basis, performing tasks such as talking and moving.<sup>82</sup> Microfibrils have the function of supporting the structure of a cell body. Tau proteins ensure the stability of microfibrils. Alzheimer's disease has the effect of chemically altering these microfibrils causing them to pair up and tangle themselves. This leads to microfilament disintegration: causing the malfunction of signal transmission and eventually cell death.<sup>83</sup>

The figure below shows the formation of Tau protein tangles.

Figure 18: The formation of Tau protein tangles<sup>84</sup>



<sup>76</sup> <http://news.bbc.co.uk/1/hi/health/7846930.stm> [Website] Last Accessed 20/12/2012

<sup>77</sup> The part of the brain responsible for memory and reasoning.

<sup>78</sup> See Appendix 10 for diagram of brain showing cerebral cortex

<sup>79</sup> <http://news.bbc.co.uk/1/hi/health/7846930.stm> [Website] Last Accessed 20/12/2012

<sup>80</sup> Ibid.

<sup>81</sup> See Appendix 11 for diagram.

<sup>82</sup> <http://biology.about.com/od/anatomy/a/aa031408a.htm> [Website] Last Accessed 20/12/2012

<sup>83</sup> [http://www.pueblo.gsa.gov/cic\\_text/health/alz-cure/alz-cure.htm](http://www.pueblo.gsa.gov/cic_text/health/alz-cure/alz-cure.htm) [Website] Last Accessed 20/12/2012

<sup>84</sup> <http://www.bioedonline.org/hot-topics/alzheimers-disease.cfm> [Website] Last Accessed 20/12/2012



Alzheimer's disease severely damages brain cells. The decrease in brain activity increases until the person affected can no longer perform tasks, such as remembering how to brush their teeth. There are sometimes drastic personality and behaviour changes.<sup>85</sup> Brain shrinkage and the enlarging of ventricles are the main causes of brain damage. Accompanied by the loss of effective neurons, the majority of electrical signals fail to transmit properly.

The figures below show the physical effect that Alzheimer's disease has on the brain and neurons.

Figure 19: Healthy and unhealthy neurons, and progression from a healthy to a severely diseased brain<sup>86</sup>

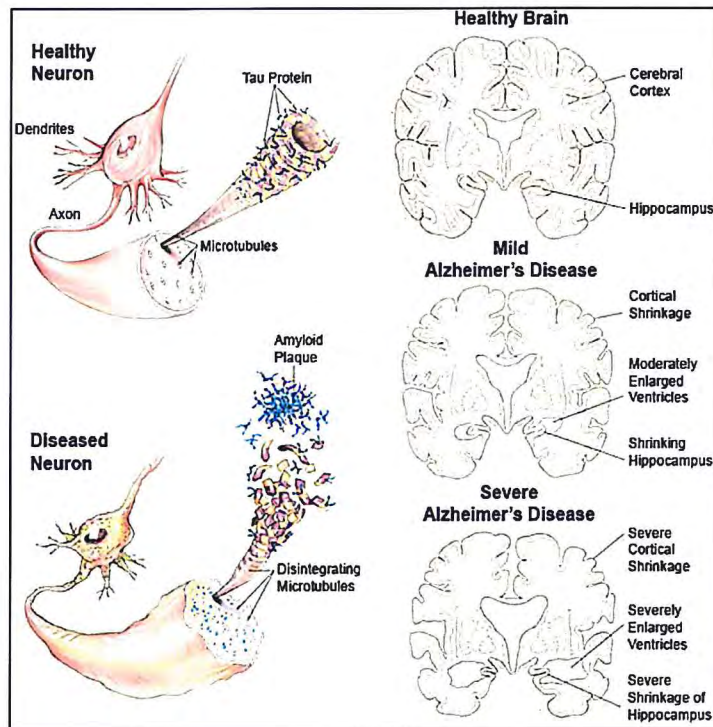
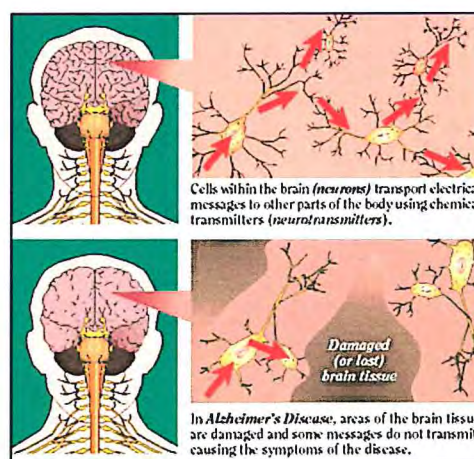


Figure 20: The progression of Alzheimer's disease progresses; the death of neurons and the disruption of the transmission of electrical signals<sup>87</sup>



<sup>85</sup> [http://www.pueblo.gsa.gov/cic\\_text/health/alz-cure/alz-cure.htm](http://www.pueblo.gsa.gov/cic_text/health/alz-cure/alz-cure.htm) [Website] Last Accessed 19/12/2012

<sup>86</sup> <http://www.doctorssupport.org/list/alzheimers-disease-symptoms-alzheimers> [Website] Last Accessed 19/12/2012

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## Future Research

Neurodegenerative diseases are fatal<sup>88</sup> and treatment for them consists of reducing pain and aggressive behaviour<sup>89</sup>. Medical research has been focused on such areas because solving these problems lead to practical solutions, for example, the pain relief improving the care for patients. These diseases are predicted to affect more and more of society.<sup>90</sup> Thus increasing a need to find a cure for these diseases; in particular the diseases that are included under the term dementia.

Medical research has enabled scientists to gain molecular insight into Alzheimer's disease. This has allowed new methods in exploring effective therapeutic treatments. Scientists hope to use neurotransmitter replacements combined with medical drugs to reduce the lethal effects of the amyloid plaques. It is hoped that this would be designed specifically for individual patients, based on their genetic profile.<sup>91</sup>

Suggestions for future research have included the investigation of the formation of the long term memory. Biologists have found that sea slugs, *Aplysia californica*, forms polymers similar to PrP<sup>C</sup>. These polymers are formed at the same time as their nervous system. Scientists may be able to use information from this in memory retrieval in patients.

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<sup>88</sup> <http://www.ninds.nih.gov/disorders/kuru/kuru.htm> [Website] Last Accessed 18/12/2012

<sup>89</sup> <http://www.bmj.com/content/316/7129/446.extract> [Website] Last Accessed 18/12/2012

<sup>90</sup> <http://news.bbc.co.uk/1/hi/health/7846930.stm> [Website] Last Accessed 20/12/2012

<sup>91</sup> <http://www.bmj.com/content/316/7129/446.extract> [Website] Last Accessed 18/12/2012

## Conclusion

This essay focused on finding the exact mechanism in which prion proteins are converted into Prions. It had the objectives of exploring protein folding mechanisms and what instances cause these conversions.

Whereas the prion protein is a naturally occurring protein that is not harmful to the body, there is a variant of the Prion that is insoluble that leads to the formation of senile plaques and neurodegenerative brain diseases.

There is now a significant pressure to find a treatment that will be able to cure, rather than prolong the illnesses. Medical research has so far focused on reducing physical problems<sup>92</sup>, such as pain. While this is an important aspect of patient care, scientific knowledge is unable to explain the mechanism that is responsible for the transformation of prion proteins to Prions.<sup>93</sup>

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<sup>92</sup> <http://www.bmj.com/content/316/7129/446.extract> [Website] Last Accessed 18/12/2012

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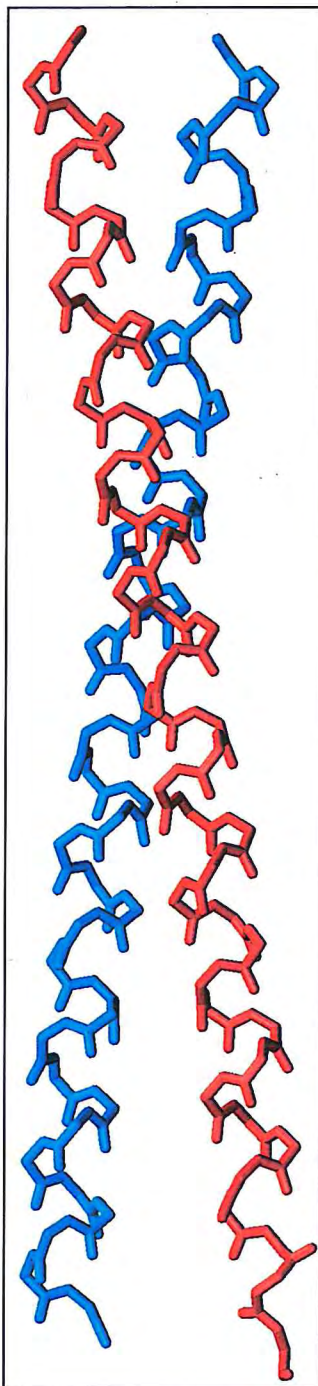
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## Appendix

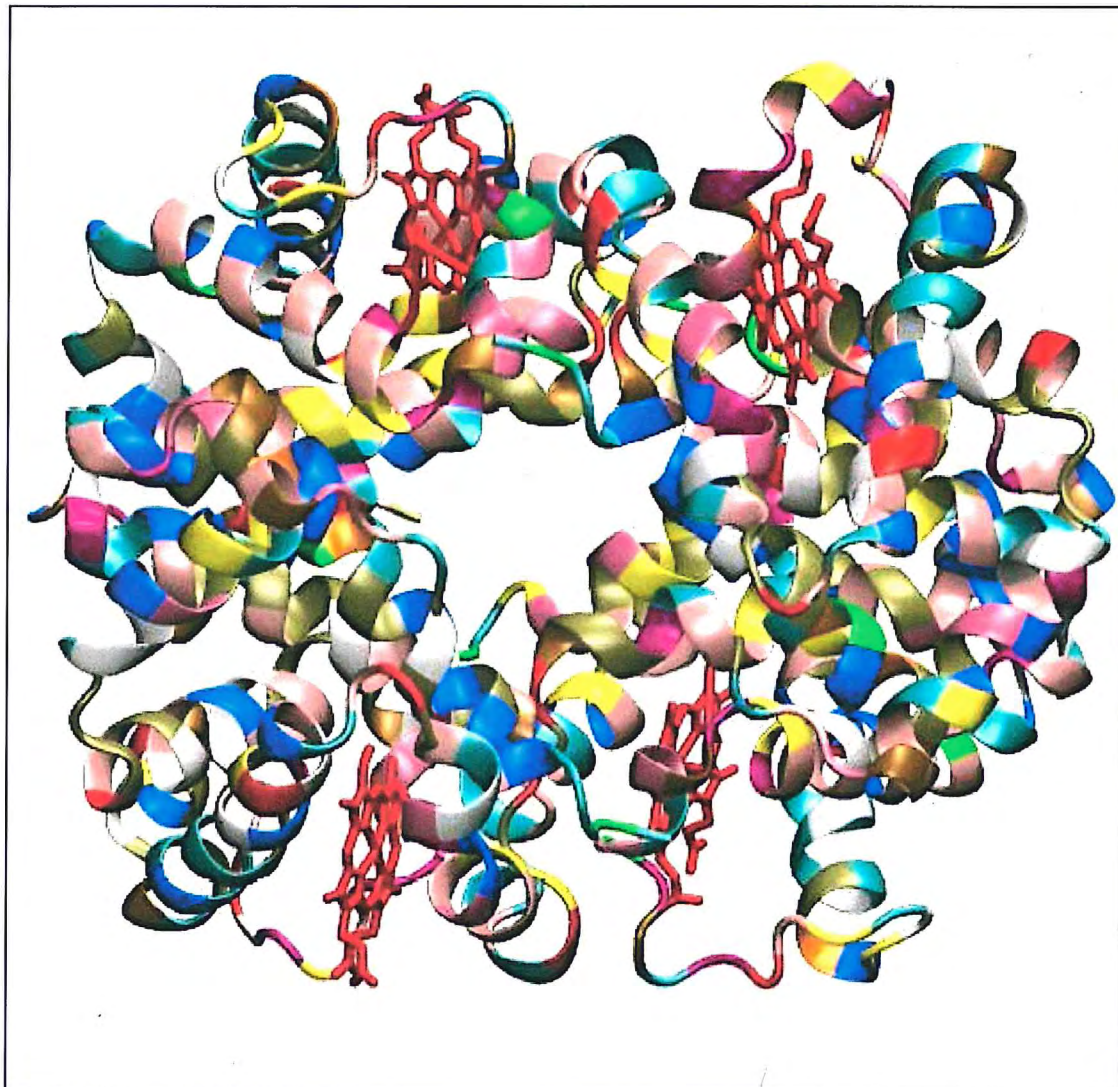
## Appendix 1: An image of a fibrous protein<sup>94</sup>



<sup>94</sup> Showing the fibrous protein  $\alpha$ -keratin, used for hair, nails and skin growth. [http://www.rose-hulman.edu/~brandt/Chem330/Protein\\_classes.pdf](http://www.rose-hulman.edu/~brandt/Chem330/Protein_classes.pdf) [Website] Last accessed 19/12/2012



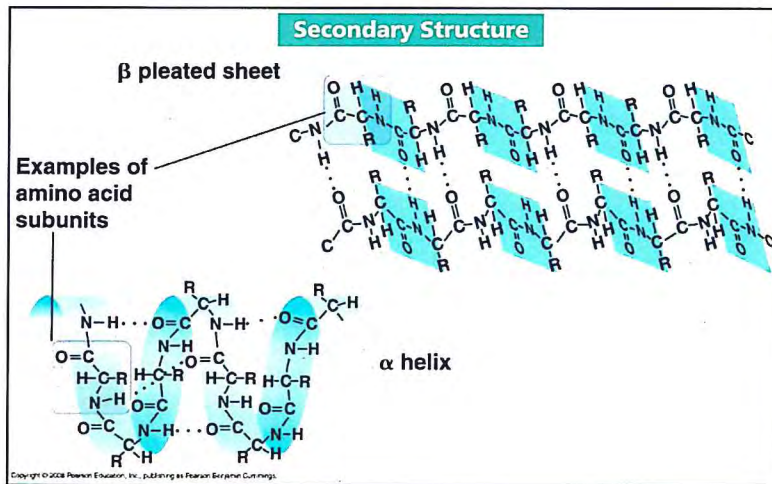
## Appendix 2: An image of a globular protein<sup>95</sup>



<sup>95</sup> Showing the globular protein haemoglobin. [http://www.rose-hulman.edu/~brandt/Chem330/Protein\\_classes.pdf](http://www.rose-hulman.edu/~brandt/Chem330/Protein_classes.pdf)  
[Website] Last accessed 19/12/2012

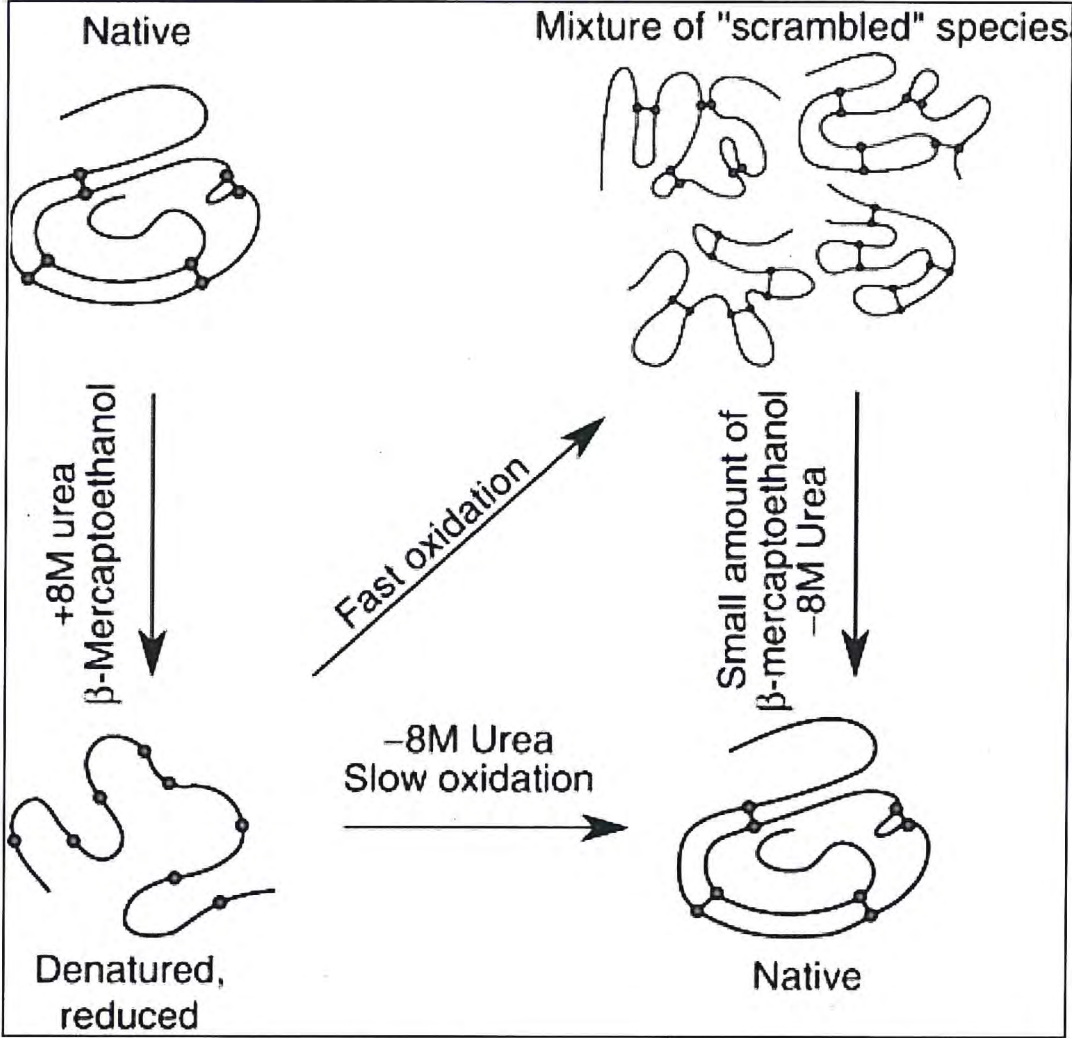


Appendix 3:  $\alpha$ -helix and  $\beta$ -pleated sheets; secondary structure protein<sup>96</sup>



<sup>96</sup> [http://www.drzolghadri.com/?attachment\\_id=139](http://www.drzolghadri.com/?attachment_id=139) [Website] Last accessed 17/12/2012

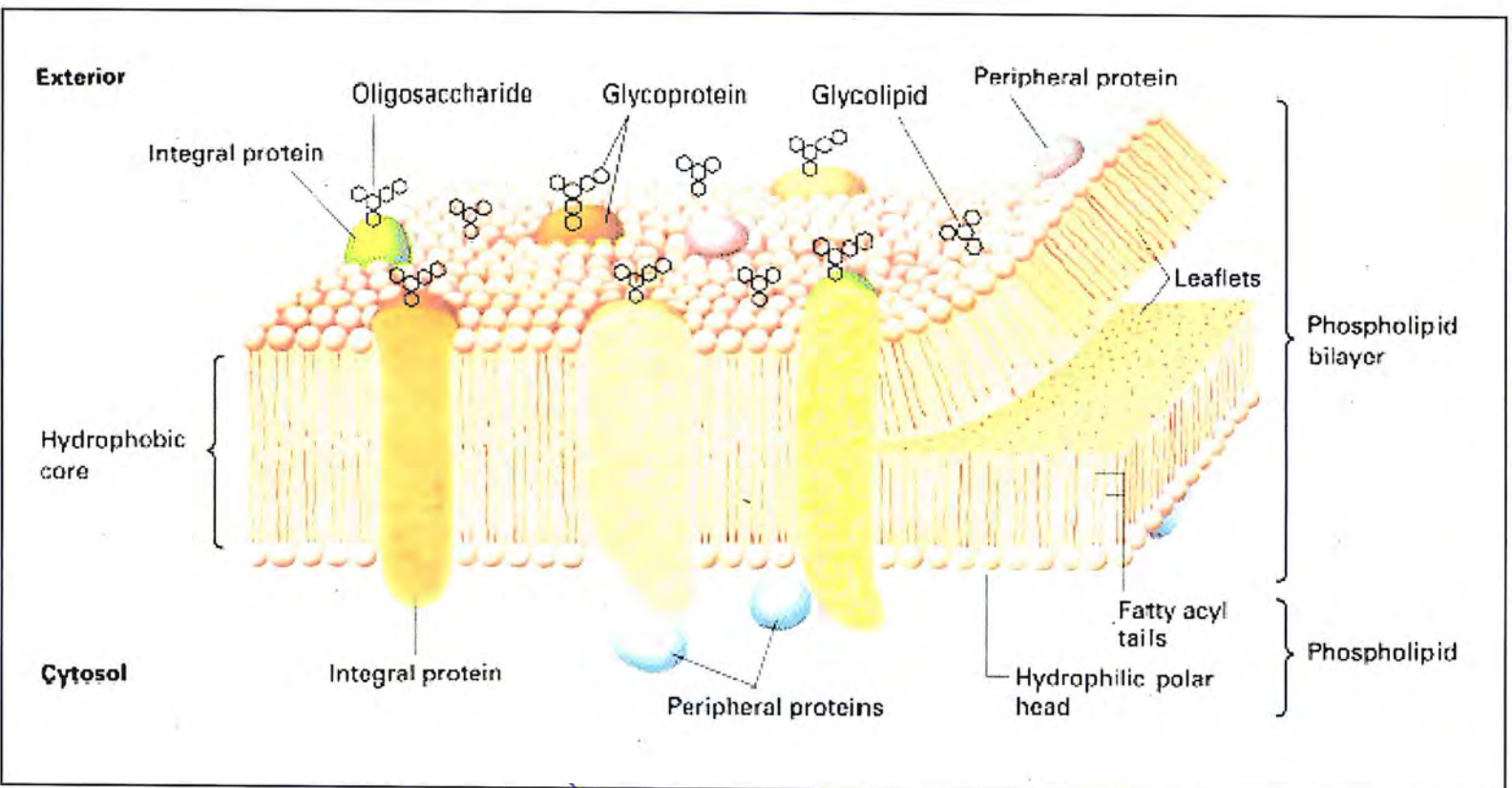
Appendix 5: Scheme of Anfinsen's experiment<sup>97</sup>



<sup>97</sup> <http://www.enzim.hu/~szia/ownpdf/foldingreview.pdf> [Website] Last accessed 18/12/2012

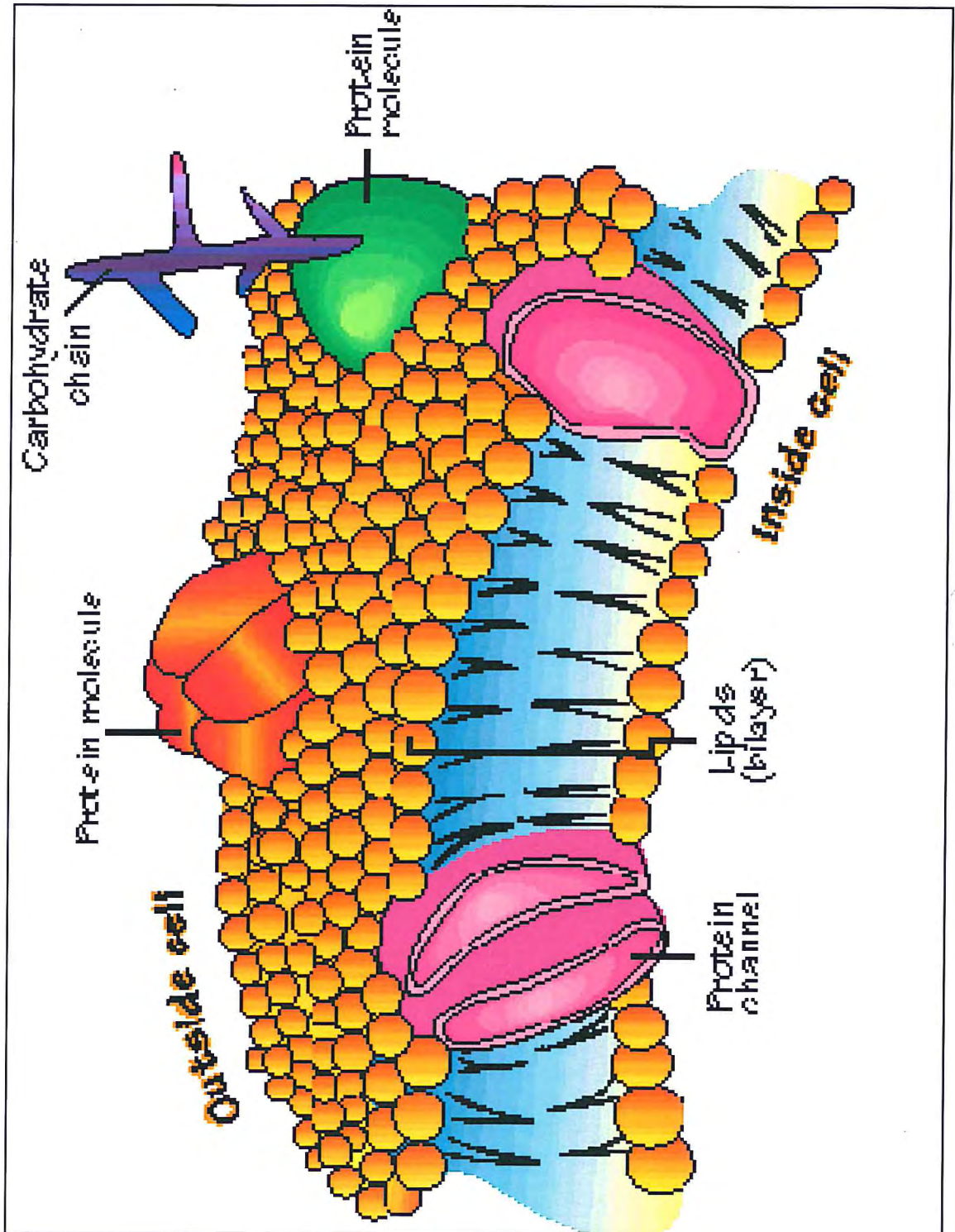


Appendix 6: A diagram of a phospholipid bi-layer<sup>98</sup>



<sup>98</sup> <http://www.unitus.it/scienze/corso/new/lezioni1.1.html> [Website] Last accessed 16/12/2012

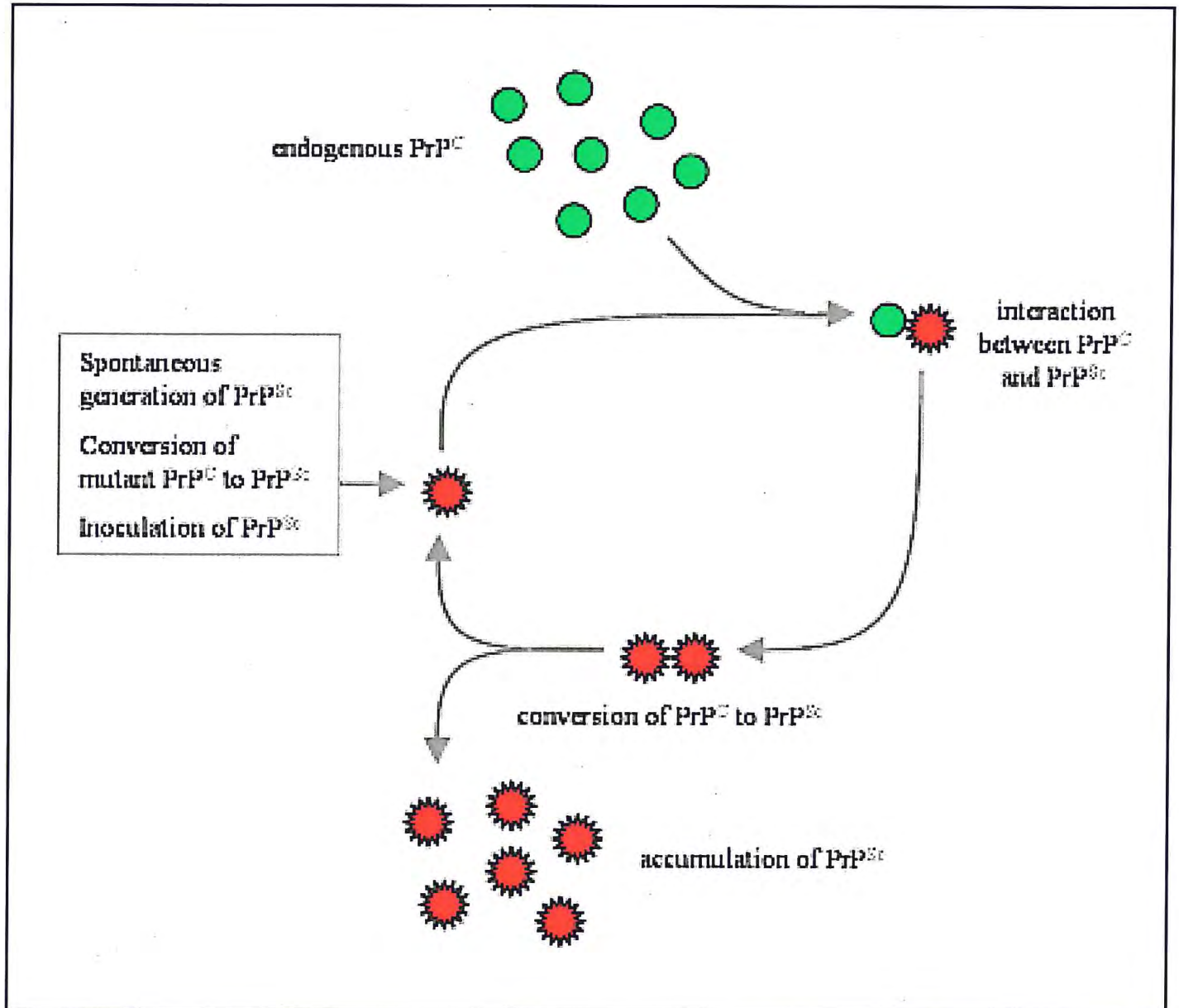
Appendix 7: A diagram of a phospholipid bi-layer<sup>99</sup>



<sup>99</sup> [http://apbio82007.blogspot.co.uk/2007\\_11\\_01\\_archive.html](http://apbio82007.blogspot.co.uk/2007_11_01_archive.html) [Website] Last accessed 16/12/2012

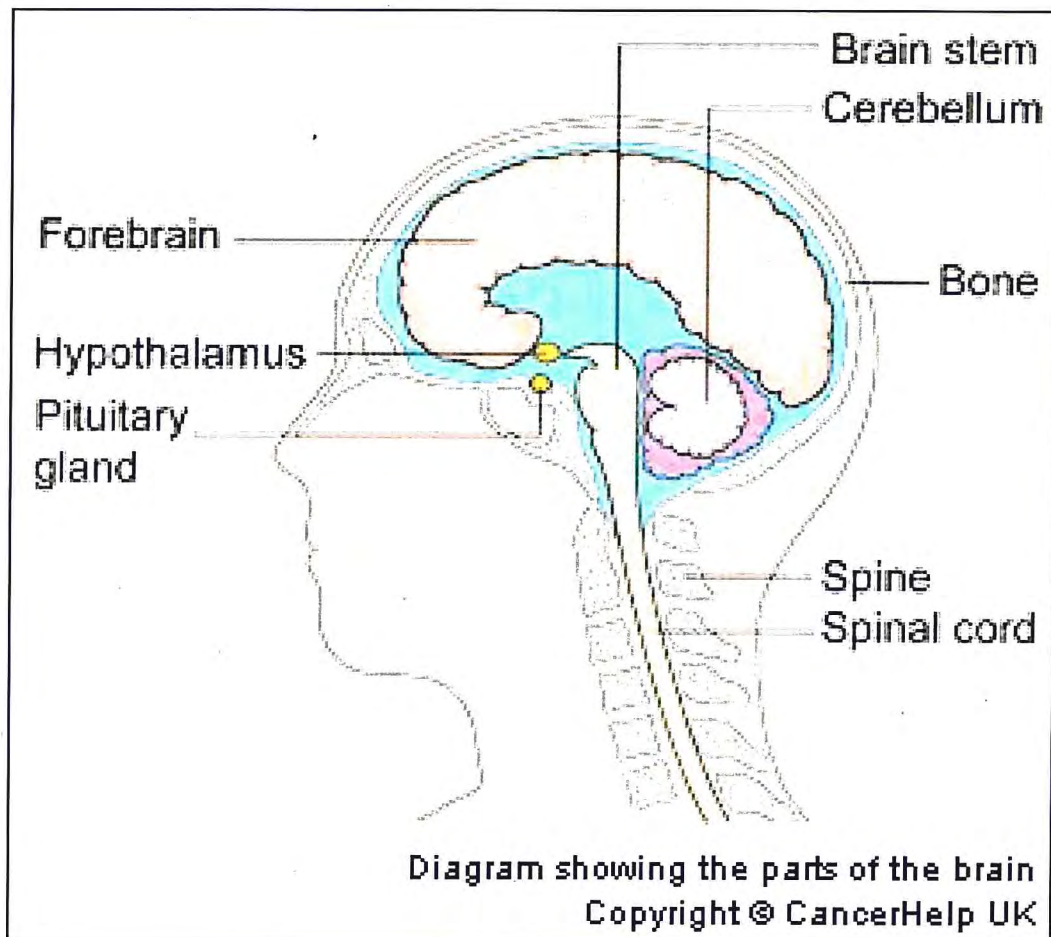


Appendix 8: Summary of Prion production, regarding current knowledge i.e. this figure does not show a mechanism<sup>100</sup>



<sup>100</sup><http://scienceblogs.com/retrospectacle/2007/02/11/basic-concepts-prions/> [Website] Last accessed 17/12/2012

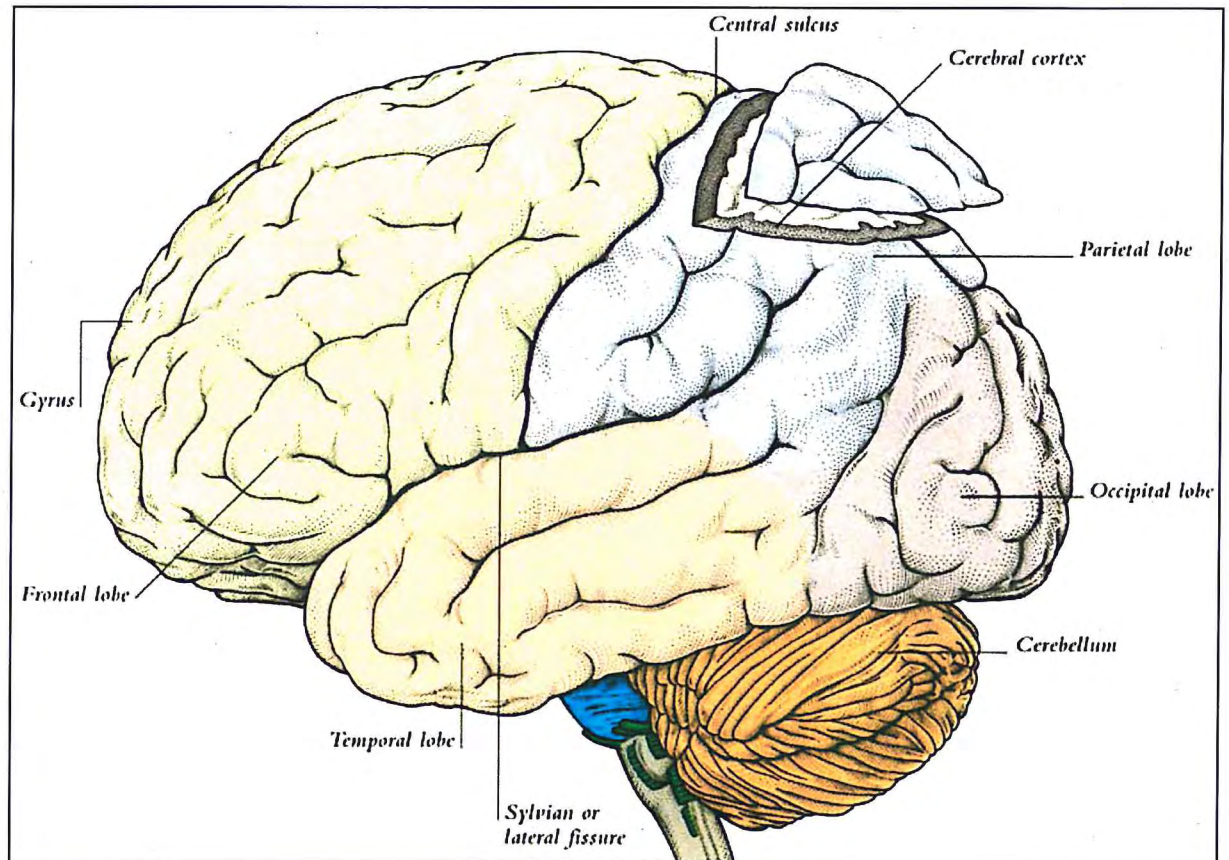
Appendix 9: A diagram of a brain showing the cerebellum<sup>101</sup>



<sup>101</sup> [http://www.google.co.uk/imgres?um=1&hl=en&sa=N&tbo=d&biw=1092&bih=522&tbn=isch&tbnid=AmHDBWp-u\\_wR5M:&imgrefurl=http://www.cancerresearchuk.org/cancer-help/type/brain-tumour/about/the-brain&docid=wYTRGAalHTAKCM&imgurl=http://www.cancerresearchuk.org/prod\\_consump/groups/cr\\_common/%2540cah/%2540gen/documents/image/crukimg\\_1000img-12313.jpg&w=300&h=270&ei=BtjpUKnaFYXKsgbekYHwAQ&zoom=1&iact=hc&vpx=4&vpy=198&dur=4630&hovh=213&hovw=237&tx=116&ty=157&sig=106772689580217206263&page=1&tbnh=140&tbnw=156&start=0&ndsp=18&ved=1t:429,r:6,s:0,i:106](http://www.google.co.uk/imgres?um=1&hl=en&sa=N&tbo=d&biw=1092&bih=522&tbn=isch&tbnid=AmHDBWp-u_wR5M:&imgrefurl=http://www.cancerresearchuk.org/cancer-help/type/brain-tumour/about/the-brain&docid=wYTRGAalHTAKCM&imgurl=http://www.cancerresearchuk.org/prod_consump/groups/cr_common/%2540cah/%2540gen/documents/image/crukimg_1000img-12313.jpg&w=300&h=270&ei=BtjpUKnaFYXKsgbekYHwAQ&zoom=1&iact=hc&vpx=4&vpy=198&dur=4630&hovh=213&hovw=237&tx=116&ty=157&sig=106772689580217206263&page=1&tbnh=140&tbnw=156&start=0&ndsp=18&ved=1t:429,r:6,s:0,i:106) [Website] Last Accessed 20/12/2012

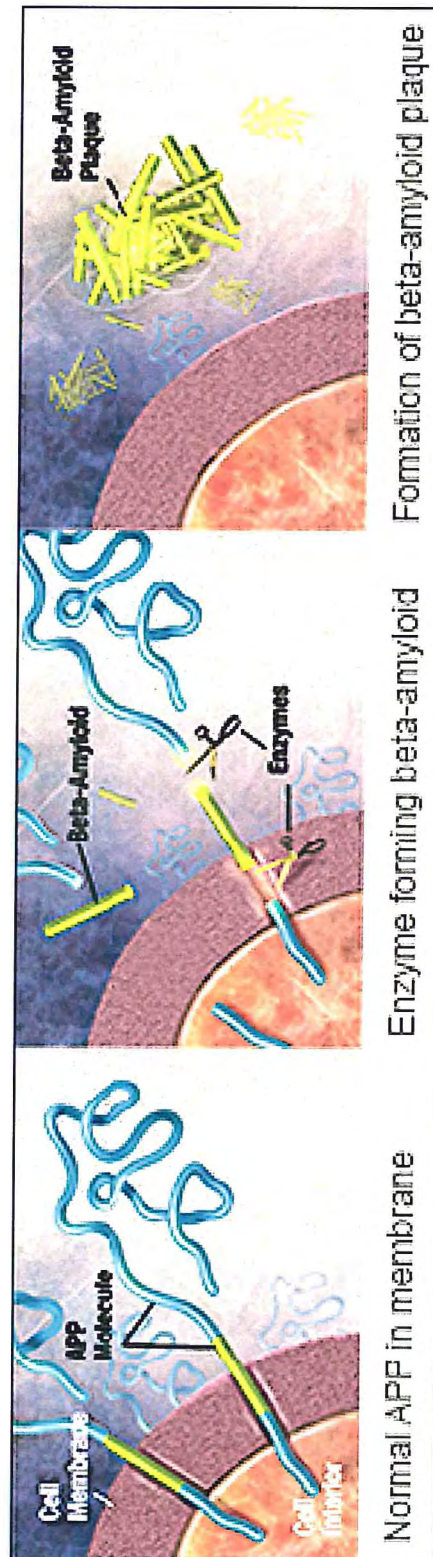


Appendix 10: A diagram of a brain showing the location of the cerebral cortex<sup>102</sup>



<sup>102</sup> [http://www.google.co.uk/imgres?um=1&hl=en&sa=N&tbo=d&biw=1092&bih=522&tbm=isch&tbnid=mL\\_MDolSr9hzOM:&imgrefurl=http://www.coheadquarters.com/coOuterBrain1.htm&docid=XYfjF-zC5gG1UM&imgurl=http://www.coheadquarters.com/coOuterBrain1x.jpg&w=800&h=568&ei=FOXpULfDAszntQa7-oCoDw&zoom=1&iact=rc&dur=466&sig=106772689580217206263&page=1&tbnh=140&tbnw=196&start=0&ndsp=10&ved=1t:429,r:1,s:0,i:157&tx=100&ty=130](http://www.google.co.uk/imgres?um=1&hl=en&sa=N&tbo=d&biw=1092&bih=522&tbm=isch&tbnid=mL_MDolSr9hzOM:&imgrefurl=http://www.coheadquarters.com/coOuterBrain1.htm&docid=XYfjF-zC5gG1UM&imgurl=http://www.coheadquarters.com/coOuterBrain1x.jpg&w=800&h=568&ei=FOXpULfDAszntQa7-oCoDw&zoom=1&iact=rc&dur=466&sig=106772689580217206263&page=1&tbnh=140&tbnw=196&start=0&ndsp=10&ved=1t:429,r:1,s:0,i:157&tx=100&ty=130) [Website] Last Accessed 20/12/2012

# Appendix 11: A diagram of $\beta$ -amyloid plaque formation in the brain<sup>103</sup>



<sup>103</sup> <http://www.bioedonline.org/hot-topics/alzheimers-disease.cfm> [Website] Last Accessed 20/12/2012