

THE LIFE CYCLE OF THE HUMAN IMMUNO-DEFICIENCY VIRUS: A USEFUL TOOL FOR TEACHING SCIENTIFIC AND NEW CHURCH PRINCIPLES IN THE BIOLOGY CLASSROOM*

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1. INTRODUCTION

In June and July 1981, the Centers for Disease Control and Prevention (CDC) reported unusual increases in numbers of a specific type of pneumonia (pneumonia pneumocystosis) in the US. These reports would mark the beginning of a new era in medicine: this was the first time the acquired immunodeficiency syndrome (AIDS) was described in the medical literature. (Morbidity and Mortality Weekly Report 1981a; Morbidity and Mortality Weekly Report, 1981b). In the almost thirty years that have elapsed since these initial reports of AIDS, there has been a considerable global effort by researchers to understand the fundamental physiological and molecular mechanisms that underlie this syndrome. We now know that AIDS is characterized by a severely weakened immune system which eventually is unable to mount an effective response to opportunistic infectious agents and tumors, invariably leading to the death of the affected individual. We also know that the primary causative agent of AIDS is the human immunodeficiency virus, HIV (Levy, 2007, 5; Stine, 2007, 16).

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All figures used in this article were made by the author.

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A virus requires a living cell, a host cell, which provides both the energy and components necessary for the viral replication. HIV infects human cells that contain a surface receptor protein known as CD4 (Dalglish *et al.*, 1984; Klatzmann *et al.*, 1984). These cells, known as CD4+ cells, include T lymphocytes, which are involved in cell-mediated immunity, an essential component of the human immune system. Once HIV is contracted, a three-stage process is initiated (Stine, 2007, 139–145). The first phase takes place shortly after the initial infection and is marked by a high viral count in the blood. This phase sometimes produces flu-like symptoms. The second phase is a time when the viral count in the blood is fairly low and the infection does not produce significant symptoms. This phase can last for several years, and an infected individual who has not been tested for HIV can be completely unaware of the infection. The final phase of an HIV infection is marked by a significant drop in the CD4+ T-cells, which renders the immune system so weakened that it is unable to produce an effective response to an invading pathogen or tumors. This, the third stage of an HIV infection, is called AIDS. The three phases of an HIV infection are nowadays collectively known as HIV disease. AIDS is thus a name given to the final stage of HIV disease.

HIV disease is a global epidemic that affects men, women, and children. Worldwide, in 2007,¹ there were approximately 33 million people living with HIV (about 15.4 million men, 15.4 million women and 2.5 million children) and the current trend is that this number is increasing every year (UNAIDS, 2007). More than 25 million people have thus far died from AIDS, making it one of the five most common causes of death around the world. In 2007 alone, 2.1 million people died from AIDS, thus averaging more than 5,700 AIDS deaths per day (UNAIDS, 2007). Especially hard hit is sub-Saharan Africa (table 1), which harbors about 68% of HIV infections in the world. The effects of HIV and AIDS on human welfare provide chilling reading: there are about 18 million AIDS orphans worldwide; the deaths of large portions of the workforce threatens the GDP of some countries; and in many places the education system is under threat as teachers succumb to AIDS (Piot, *et al.*, 2001; Stine, 2007, 312).

Although a cure for HIV disease still remains elusive, a very significant outcome of the last two and a half decades of intensive research is the illumination of the HIV life cycle—the series of steps that describe the

LIFE CYCLE OF HUMAN IMMUNODEFICIENCY VIRUS

Region	Number of infected individuals
Sub-Saharan Africa	22,500,000
East Asia	800,000
Oceania	75,000
South and South-East Asia	4,000,000
Eastern Europe and Central Asia	1,600,000
Western and Central Europe	760,000
North Africa and Middle East	380,000
North America	1,300,000
Caribbean	230,000
Latin America	1,600,000

Table 1: Approximated HIV prevalence (2007) in regions of the world (UNAIDS, 2007).

process which starts when HIV attaches and enters a new human host cell and ends with the budding, or release, of newly made virus particles from that host cell. The life cycle of HIV thus describes how the virus is replicated.

Targeting the HIV life cycle provides the basis for therapeutic intervention to HIV disease, and the more we learn about it the more sophisticated treatments can become available. Moreover, through examination of the HIV life cycle in the biology classroom, many biological processes and principles are illuminated, and furthermore, the HIV life cycle can also be used as a model to show how New Church principles apply to the natural world. It is therefore the purpose of this paper to describe a model of the

HIV life cycle and how it can be used in a New Church College classroom to illustrate scientific and spiritual principles.

2. HIV²

HIV is an enveloped retrovirus. A retrovirus has a genome that is composed of ribonucleic acid (RNA), which, following infection of the host cell, is converted to deoxyribonucleic acid (DNA)—see figures 1 and 2. Retroviruses violate the central dogma of biology: namely, the notion that genetic information only flows in the direction from DNA to RNA to protein. Hence, the name “retrovirus” (Flint *et al.*, 2004, 217–218).

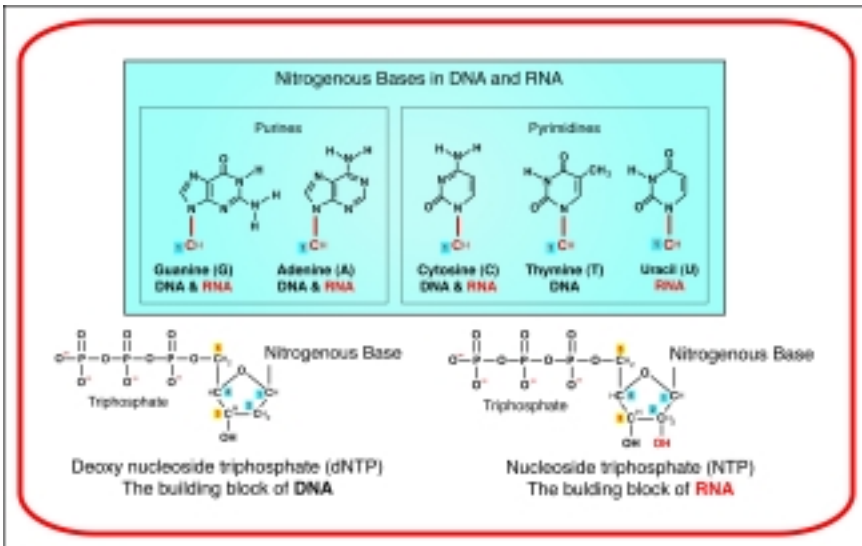


Figure 1. The structure of the building blocks in DNA and RNA. DNA and RNA are large molecules (macromolecules) that are constructed using nucleotides. A nucleotide is composed of a phosphate group, a sugar (ribose in RNA and deoxyribose in DNA) and one of four nitrogenous bases. The differences between RNA and DNA nucleotides is that the sugar in RNA contains an –OH group on carbon 2 and that the nitrogenous bases are G, C, A and U whereas the are G, C, A and T in DNA.

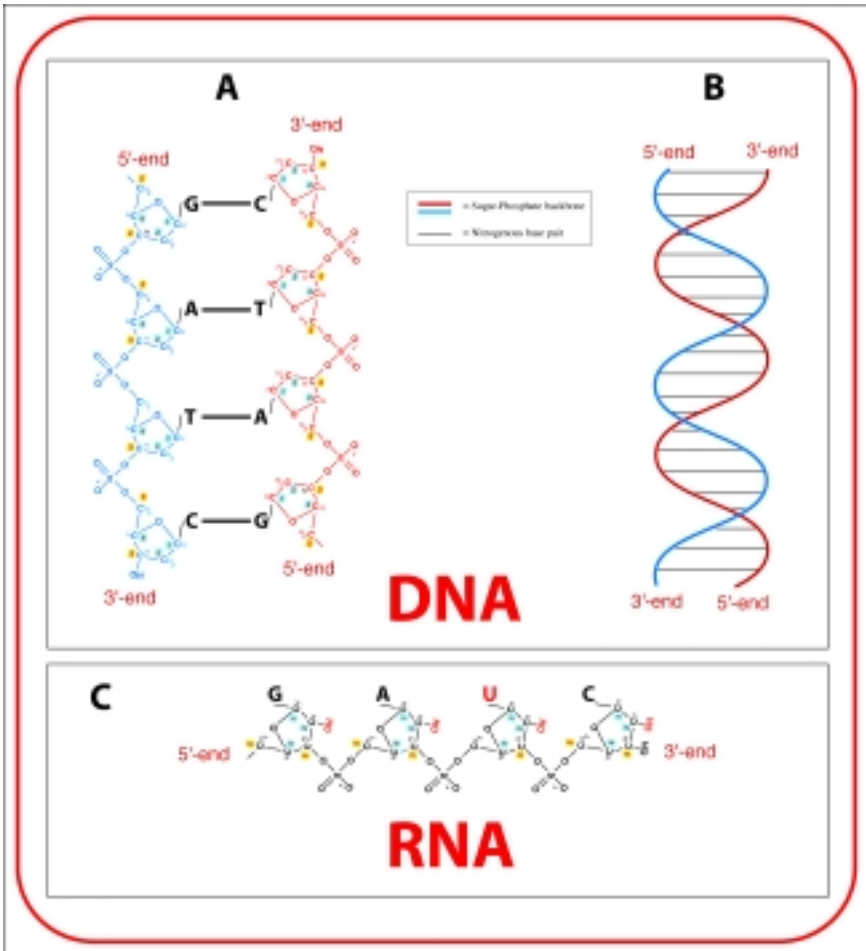


Figure 2. Simplified diagram of double stranded DNA and single stranded RNA. (A) DNA usually exists in a double-stranded form. The nitrogenous bases on the other strand binds to the nitrogenous bases on the other strand. This is called base-pairing and follow the Watson-Crick rules: A base-pairs with T and G base pairs with C. (B) The structure of a double-stranded DNA molecule is a helix. (C) RNA is usually found as a single-stranded molecule.

2.1 The structure of HIV-1³

A simplified model of the structure of a HIV-1 virion⁴ is shown in figure 3. The outermost covering of the virion is a lipid bilayer, called the

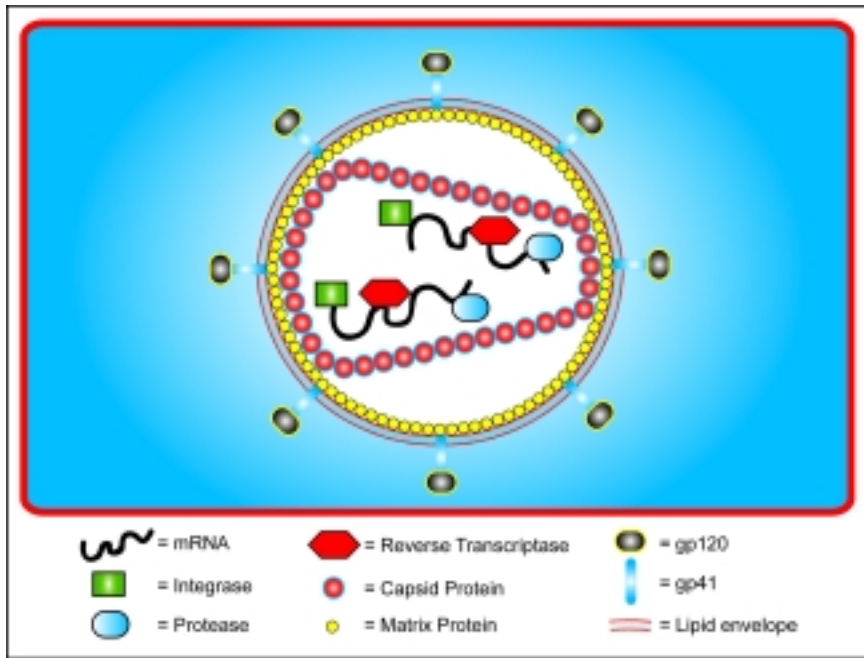


Figure 3. The structure of HIV-1. This simplified model shows a mature HIV-1 virion in cross-section. The viral genome (the genetic material), a single-stranded RNA molecule, and the three viral enzymes (catalysts) integrase, and reverse transcriptase are enclosed by the conical core that is composed of the structural capsid protein. Outside the core is another protein layer that is composed of the structural matrix protein. The outermost layer is the envelope, through which projects the gp120/gp41 (gp = glycoprotein) proteins that are involved in attachment to and fusion with the human host cell.

envelope, which is derived from the plasma membrane⁵ of the human host cell where the virus was produced (see section 2.2 below).

The outer surface of the HIV-1 virion contains a type of surface proteins composed of the two peptides gp41 and gp120. It is the gp120 portion of this complex that interacts with the CD4 receptor on the human host cell, which marks the first step in the life cycle of HIV-1 (Freed *et al.* 1995; Hope *et al.*, 2000).

Underneath the lipid envelope of HIV-1 there are two different layers of protein shells. The outer layer is known as the matrix and is made up of the MA protein. The inner layer is called the capsid and is composed of the CA protein. The capsid surrounds the core, which, in turn, contains two

copies of the viral RNA genome and associated viral proteins including reverse transcriptase and integrase.

2.2 The life cycle of HIV-1

The life cycle of HIV-1⁶ comprises the series of events that begins with the attachment of the virus to the CD4 receptor on the host cell surface, and ends with the production of new viral particles that bud off from the new host cell. The basic steps of the HIV-1 life cycle are outlined in table 2.

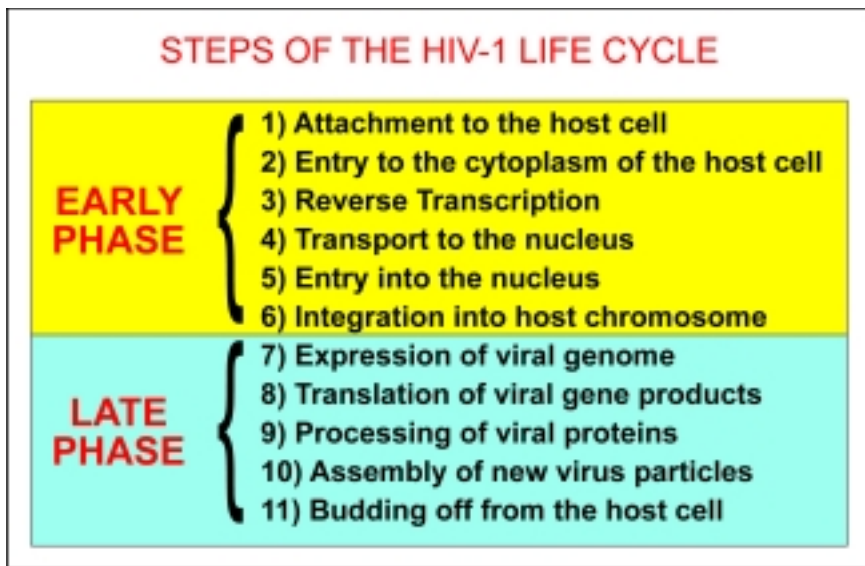


Table 2. The steps of the HIV-1 life cycle.

The first six steps of the HIV-1 life cycle describes the series of events from the initial attachment to the human host cell through the steps culminating with the integration of the viral genome within the host genome. These six steps are often referred to as the early phase of the HIV-1 life cycle, whereas the steps from the expression of the viral genome to when new virus particles bud off from the host cell are called the late phase.

The first step of the HIV-1 life cycle is attachment to the host cell. This process begins when the gp120 protein on the viral surface binds to a CD4 receptor on the host cell surface by a mechanism that involves conformational changes (i.e., changes in the three-dimensional structure) in both the CD4 receptor and the gp120 protein. For successful HIV-1 binding to the host cell, the gp120 protein must then also bind to a co-receptor, such as the chemokine receptors CCR5 or CXCR4. The co-receptor protein is a part of the host cell. The importance of co-receptor binding for a successful HIV-1 infection is underlined by the findings that HIV-1 infectivity is compromised in individuals that harbor mutant (not functioning) CCR5 proteins, and that agents that bind to CCR5 and CXCR4 (and thus block HIV-1 from binding to these receptors) reduce viral infectivity (Berger *et al.*, 1999; Carrington *et al.*, 1999; Schols, 2004).

After successful attachment to the host cell, HIV-1 is able to enter into the cell by a process that involves fusion of the viral envelope with the plasma membrane of the host cell. Once the virus is inside the host cell, the viral single-stranded RNA genome is converted into double-stranded DNA. This process, called reverse transcription, is an essential step in the HIV-1 life cycle because it prepares the viral genome for the subsequent integration into the host chromosome. (Flint *et al.*, 2004, 218–230; Götte *et al.*, 1999).

Reverse transcription is catalyzed by the virally encoded enzyme reverse transcriptase, an RNA- and DNA-dependent DNA polymerase (Baltimore 1970; Temin *et al.*, 1970). The function of DNA polymerases is to synthesize DNA. In brief, they do this by adding nucleotides (the building blocks of DNA) to a nascent DNA strand. In this process, the DNA polymerase uses the nucleotide sequence on a template strand to guide its DNA synthesis. Occasionally, however, a DNA polymerase accidentally incorporates an incorrect nucleotide during DNA synthesis. This, if left uncorrected, results in a permanent inheritable change—a mutation—in the DNA. To counteract such errors many DNA polymerases contain a proofreading activity that enables them to assess the nucleotides they have added. If a mistake has been made, these DNA polymerases are able to remove the incorrect nucleotide and replace it with the correct one. A notable characteristic of HIV-1 reverse transcriptase is that it lacks such a proofreading activity (Flint, *et al.*, 2004, 225). Therefore, if any nucleotides

are incorrectly incorporated during reverse transcription they will remain in the newly made double-stranded DNA molecule that now represents the HIV-1 genome. The lack of proofreading by reverse transcriptase is indeed the fundamental reason why HIV-1 is so successful in evading the human immune system and why a successful vaccine or a cure for HIV disease have not yet been developed (see section 3 below)⁷.

When reverse transcription is completed, the viral genome (now a double-stranded DNA molecule) and associated proteins enters the nucleus of the host cell. The viral genome is then integrated into the host chromosome. Following integration, the virus thus exists as a part of the genome of the human host. The virus is now referred to as a provirus.

Integration is a three-step process of by which the HIV-1 genome becomes incorporated into the human host cell genome. First, the viral DNA and the host chromosome are processed to prepare them for integration. Second, the viral and host cell DNA are joined together, and thirdly, the two DNA molecules are chemically bonded together. The final step of integration is referred to as post-integration repair. The processing and joining events of retroviral integration have been successfully reconstituted using *in vitro*⁸ assays (Craigie *et al.*, 1990; Katz *et al.*, 1990). These studies demonstrated that the integrase protein alone is sufficient for the processing and joining events of integration.

Although retroviral integration has been well characterized *in vitro*, the nature of the integration mechanism *in vivo* is not fully understood. This is not surprising as the environment is much more complex in a living cell compared to the environment in a test tube during an *in vitro* assay. Nevertheless, recent research provides us with data that enables a model of HIV-1 integration *in vivo* to be proposed. Perhaps the biggest difference between the *in vitro* reconstitution assays and the studies of integration *in vivo* is that there is evidence that HIV-1 *in vivo* utilizes many different host proteins to complete the process of integration. The proposed roles for host proteins in HIV-1 integration include post-integration repair (repairing the host chromosome following integration) and facilitating the interaction between the viral DNA and the host chromosome (Jacque *et al.*, 2006; Maertens *et al.*, 2003).

An interesting and intriguing turn in our understanding of retroviral integration came in 1999 when it was first reported that the DNA-depen-

dent protein kinase (DNA-PK)—which is composed of the three proteins Ku70, Ku80, and DNA-PKcs—is involved in retroviral integration *in vivo* (Daniel *et al.*, 1999). DNA-PK is an essential component of the non-homologous end joining (NHEJ) pathway of DNA repair. NHEJ is utilized to repair double-stranded breaks in DNA produced either by exogenous DNA damaging agents such as ionizing irradiation or endogenous recombination events such as V(D)J recombination, (the recombination process that generates mature B and T⁹ cells in the vertebrate immune system). Central players in the NHEJ repair pathway are the proteins Ku70, Ku80, DNA-PKcs, XRCC4, DNA ligase IV and Artemis (Moshous *et al.*, 2001; Bryntesson, 2002, 46-63; Meek *et al.*, 2004).

The current line of evidence for NHEJ involvement in integration includes the findings that integration is impaired but not ablated in cells that lack functional NHEJ repair proteins (Daniel *et al.*, 1999; Jeanson *et al.*, 2002; Waninger *et al.*, 2004; Lau *et al.*, 2004; Daniel *et al.*, 2004). The residual levels of integration in NHEJ-deficient cells suggest that a NHEJ independent mechanism is also involved in integration (Daniel *et al.*, 1999). In 2004, it was demonstrated that complementing DNA-PKcs-deficient (i.e. mutant) cells with a wild-type (i.e. normal) DNA-PKcs gene restore integration to normal levels (Daniel *et al.*, 2004). Thus, integration levels can be restored to normal in DNA-PK mutant cells when these cells are supplemented with a normal DNA-PK protein. This finding therefore provides strong evidence that DNA-PK is required for efficient integration. Another observation that supports NHEJ involvement in retroviral integration is that some NHEJ-deficient cells undergo apoptosis (cell death) following infection by retroviruses (Daniel *et al.*, 1999; Li *et al.*, 2001).

If NHEJ is involved in retroviral integration, then the question arises as to what exact function NHEJ may be fulfilling in this process. One possibility is that NHEJ is directly involved in post-integration repair following the joining reaction by integrase (Daniel, 2006). According to this model, if a component of the NHEJ repair pathway is lacking in a cell, then the chromosomal DNA at sites of integration is left unrepaired. The DNA damage response pathway (figure 4) in the cell senses unrepaired DNA as DNA damage, which can trigger events such as apoptosis or cell cycle arrest (Bryntesson, 2002, 34–38; Durocher *et al.*, 2001; Zhou *et al.*, 2000). The unrepaired DNA at the site of integration in NHEJ-deficient

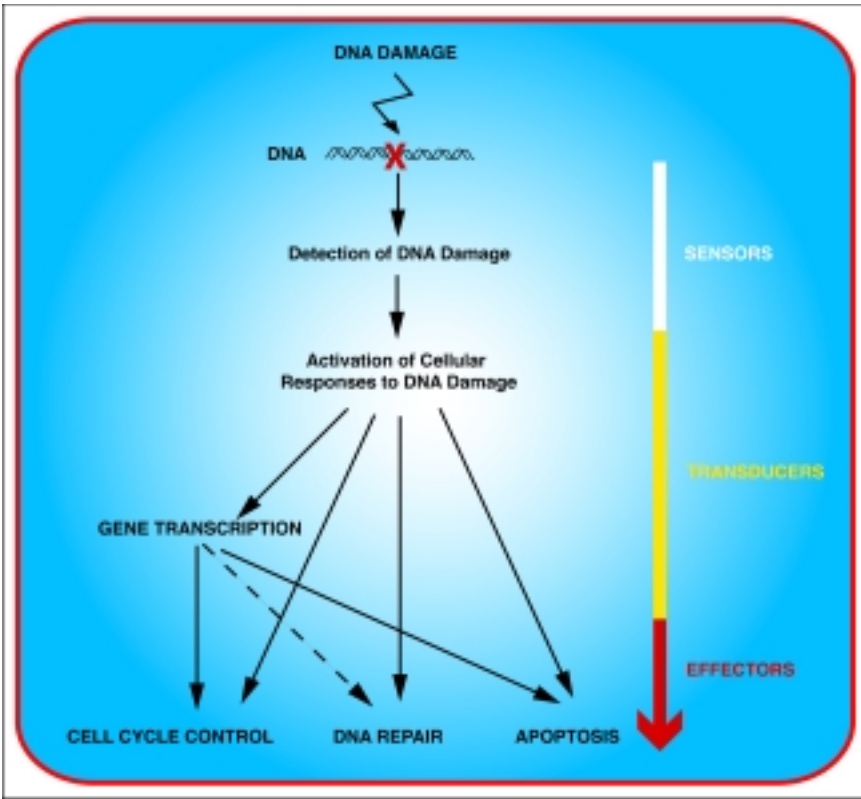


Figure 4. The DNA-damage response pathway is a collective name for the many cellular mechanisms that are involved in sensing, transducing and carrying out the cellular responses to DNA damage. Responses include, alteration in gene transcription, apoptosis, cell cycle arrest and initiation of DNA repair. The transducers in the DNA damage response pathway are the proteins that activate cellular responses to the DNA damage by means of signaling to the downstream effectors. Thus the transducers form the link between the initial sensing of DNA damage and the final response that is carried out by the cell.

cells could thus explain the reason why these cells undergo apoptosis following HIV infection (Daniel *et al.*, 1999).

In addition to the NHEJ repair pathway, there is also evidence that the DNA damage response pathway itself is involved in retroviral integration. ATM (ataxia telangiectasia mutated) is a key player in transducing signals in the DNA damage response pathway (Bryntesson, 2002, 34–38; Durocher *et al.*, 2001; Zhou *et al.*, 2000). The first line of evidence for ATM involve-

ment in retroviral integration came in 2001 when it was demonstrated that the residual integration seen in DNA-PK-deficient cells, could be completely abolished in ATM-deficient cells when the DNA-PK inhibitor Wortmannin was used (Daniel, *et al.*, 2001). Thus, this study shows that there is no integration occurring at all when the DNA-PK activity and ATM are simultaneously missing from a cell. These results, therefore suggest that both DNA-PK and ATM are necessary for normal levels of retroviral integration. It was also reported recently that ATM is essential for efficient integration in a study that demonstrated that the ATM-specific inhibitor KU-55933 reduces HIV-1 integration significantly (Ariumi *et al.*, 2005; Dehart, *et al.*, 2005; Lau *et al.*, 2005). It was also recently reported that another DNA damage response protein, Nijmegen breakage syndrome protein 1 (NBS1) recruits ATM to the site of post-integration repair (Smith *et al.*, 2008). Another important DNA damage response pathway protein, ATR (ATM and Rad related), has also been implicated in retroviral integration (Daniel *et al.*, 2003).

The late phase of the HIV-1 life cycle comprises of the steps involved from the expression of the viral genes from the provirus to the assembly and budding off from the host cell of HIV-1 virions (Stine, 2007, 41–45). These steps requires the usage of several host cell components including the proteins RNA polymerase to transcribe the viral genes, and the host cell protein translation machinery to make viral protein.

3. THE HIV-1 LIFE CYCLE AS A VEHICLE FOR ILLUSTRATING GENERAL AND SPECIFIC SCIENTIFIC CONCEPTS

The HIV-1 life cycle and its consequences are a very useful vehicle for illustrating scientific concepts. A variety of biological and biochemical mechanisms ranging from relatively simple general discussion themes to very complex cutting edge scientific findings and challenges can be explored.

Every aspect of the HIV-1 life cycle can be used in the classroom to illustrate important biological mechanisms and principles. The initial attachment of the viral gp120 protein to the host cell CD4 receptor, for instance, is a good example of the principles of protein-protein interactions and the importance of conformational changes that proteins undergo

when they perform their function. Another example is viral reverse transcription and how it can be contrasted with regular cellular DNA synthesis – an exercise that reinforces the understanding of how DNA is made in living cells. By comparing reverse transcription with regular cellular DNA synthesis, students more fully appreciate the complexities of nucleic acid synthesis.

There are many more examples of how the HIV-1 life cycle can be used in the classroom to illustrate scientific principles and concepts and equip students with the tools necessary for being discerning scientists. Here the focus is on three specific examples: natural selection, drug development, and understanding conflicting reports in the scientific literature.

3.1 Natural selection and the HIV-1 life cycle

Although HIV research has made considerable progress in the last 25 years, no one has yet developed a successful cure or vaccine for HIV disease. HIV-1 is a master of evading the human immune system that normally is excellent in recognizing and dealing with pathogens. Thus infected individuals cannot rid themselves of the virus. What characteristics of the virus enable it to be so successful in evading both medical treatment and our own immune system? The error-prone viral DNA synthesizing mechanism reverse transcription is primarily what enables the virus to be a shape shifter (see below). This mechanism presents a perfect opportunity to explore the concept of natural selection.

As described above, reverse transcriptase, the enzyme that converts the viral genome from a single-stranded RNA molecule to a double-stranded DNA molecule, lacks a proofreading activity. This means that reverse transcriptase is unable to correct itself if it makes a mistake. In other words, a misincorporated nucleotide will remain in the DNA strand that reverse transcriptase synthesizes (figure 5). This results in a mutation—a change in the nucleotide sequence of the HIV-1 genome. A mutation, in turn, can alter the structure of the protein the HIV-1 gene codes for.

One reason why the immune system is very effective in a healthy individual is because it contains a multitude of components, each of which recognizes with extreme specificity a certain structure on a pathogen such as a virus. This ability to recognize a pathogen with specificity makes the

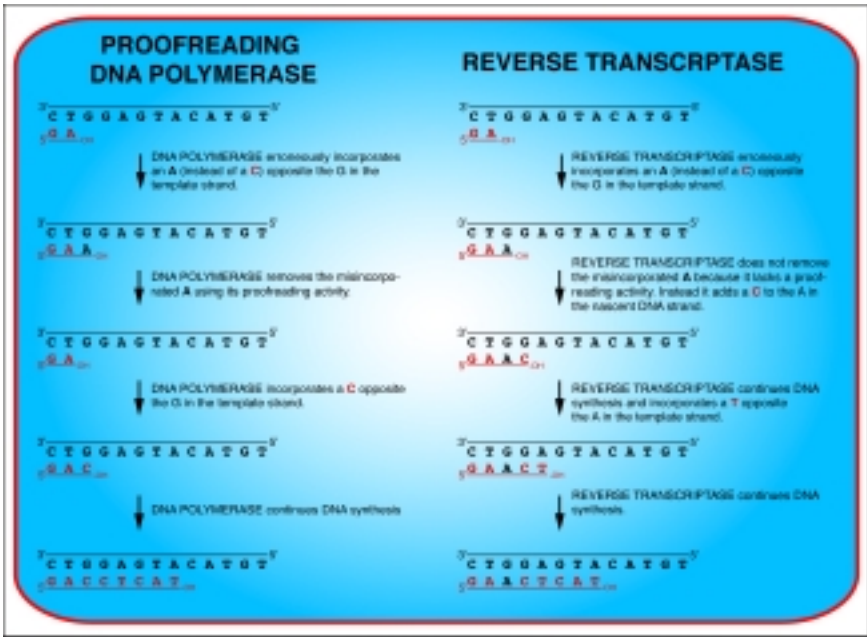


Figure 5. Comparison between a proofreading DNA polymerase (left) and reverse transcriptase (right).

immune system able to fight infections with high precision. Moreover, the immune system is capable of learning what a new pathogen looks like (i.e., what structure it has). Once the immune system knows what a certain pathogen looks like, it is capable of mounting a swift and effective response should the pathogen infect the individual again. For example, if a person has had a rubella infection (German measles) as a child, her immune system will ensure that a second rubella infection will not result in German measles symptoms as the virus will be targeted and destroyed by the immune system immediately upon infection.

Drugs that target viral components require that the virus maintain a specific structure over time. Similarly in order for the immune system to recognize a virus, its structure has to be static. Vaccines trigger immune responses; unless the immune system recognizes the virus, vaccines are of no use. But, as mentioned above, mutations induced by reverse transcrip-

tion can lead to changes in the structure of HIV-1. These mutations are the reason why the immune system, drugs, and vaccines fail to effectively target the ever-changing virus.

The ability of HIV-1 to mutate and undergo structural changes that elude the immune system and medical intervention is a very good example of natural selection in action. Natural selection, originally described in 1859, is the mechanism by which certain organisms survive in a given environment because they are more “fit.” They are more likely to survive and reproduce to pass on their successful genes to the next generation. The environment is said to exert a selective pressure on organisms, so only the fittest ones survive.

As with any biological concept, it is very useful to have students examine and discuss specific examples of natural selection in the classroom. The evolution¹⁰ of bacterial antibiotic resistance¹¹ is an excellent example to illustrate natural selection in action (Barlow, *et al.*, 2005). The students are asked to identify the selective pressure (the antibiotic in this example) and the characteristics that enable living organisms (the bacteria in this example) to survive the selective pressure (e.g., a gene that encodes a protein which blocks the action of the antibiotic). This is sometimes a very straightforward exercise. For example, if an animal is born with an ability to be more successful in avoiding predators by being able to run faster, then this animal has a greater chance to survive the selective pressure and, as a consequence, be able to reproduce and pass its genes on to the next generation. Students usually have no problem with understanding that the predator exerts the selective pressure, and the ability to outrun the predator is the beneficial characteristic that makes the animal able to survive (survival of the fittest) in this situation.

Fundamentally, the life cycle of HIV-1 provides a very straightforward example of natural selection in action. The selective pressure is exerted by the immune system, drugs and vaccines, and the beneficial characteristic that enables the virus to escape the selection pressure is that it is able to change its structure. This simple notion is a good starting point in the biology classroom, and depending on the level of the biology course, the notion can be developed to include a more detailed description of the molecular biological and biochemical mechanisms that are involved.

For example, the type of mutations in the HIV-1 genome that confer selective advantage to the immune system can be discussed in terms of how and why they work. In an upper level course in molecular biology or biochemistry, students can examine the recent finding that the G333D mutation in reverse transcriptase confers resistance to the anti-HIV-1 drugs azidothymidine, also known as zidovudine (AZT) and lamivudine (Zelina *et al.*, 2008). Students would be asked to explain *how* it is that the G333D mutation in the reverse transcriptase protein can make two different drugs ineffective. Furthermore, examining mutations in the reverse transcriptase protein itself offers an opportunity for discussing the thought-provoking concept that the error-prone reverse transcriptase generates mutations in its own gene (i.e. the reverse transcriptase gene which is part of the HIV-1 genome).

Taken together, a classroom investigation into the survival of HIV-1 in the human body strengthens students' knowledge and understanding about natural selection, and in the process of doing so also provides an opportunity to learn more about biological mechanisms that are involved in this process.

3.2 Understanding approaches to anti-HIV-1 therapy

The preceding section described why HIV-1 is a master of surviving the selective pressures that it encounters in the human body; a successful anti-HIV-1 drug is always subjected to the risk of becoming ineffective due to the evolution of the virus. It is therefore a major challenge to develop treatments for HIV disease. A useful approach is to provide patients with drug cocktails (several different drugs applied together), a type of treatment that increases the chance that at least some of the components of the drug cocktail will be effective in inhibiting the HIV-1 life cycle. It is a very useful exercise for students to examine the difference between how a single drug and a drug cocktail works, and then explain why the drug cocktail has a better chance to work in the long run.

Whereas most HIV-1 treatments are designed to target viral components, there is now a growing field of study that is exploring the possibility of blocking the activity or function of host cell proteins that HIV-1 utilizes

during its life cycle. Targeting such host proteins is an attractive therapeutic approach because host cell proteins are much less likely to undergo mutations than the viral proteins. Hence, if a drug that targets a host cell protein is found to inhibit HIV-1 infection, it is likely to be more effective in the long run than drugs designed against viral components. Of course, specific care has to be taken to ensure that blocking the function of a specific host protein does not affect the host cell – and thus the individual – adversely.

As described in section 2, HIV-1 utilizes co-receptors when attaching to the host cell. Research groups have recently designed drugs that bind to the co-receptors thus blocking HIV-1 from binding to the host cell. This is a good example of host proteins that have been the targets for anti-HIV-1 drug development (Schols, 2004). In order to understand this particular concept, the students do not need extensive background into the HIV-1 life cycle. All they need to appreciate is that the virus requires a certain protein in order to attach to the human host cell; if this protein is blocked by a drug, then the virus is unable to bind properly. Therefore the host cell escapes infection. Utilizing host proteins is a suitable anti-HIV-1 approach for discussion with college biology students at an introductory level in the process of familiarizing them with the mechanisms of viral actions in the human body.

Another approach that targets host proteins is the ongoing research into inhibitors of the DNA repair and DNA damage response proteins that HIV-1 appears to utilize during the integration step of its life cycle. Understanding these host proteins requires a thorough understanding of the molecular biology of the cellular responses to DNA damage. Therefore, this example is better suited for upper class students. The discussion can begin with focusing on the roles and functions of inhibitors of HIV-1 and host cell proteins. Then, a discussion of why it is important to administer anti-HIV drugs continuously for a prolonged time during an infection is a logical second step. Often the first answer that the students have is that the purpose of the treatment is to destroy as much as possible—ideally all¹²—of the viral population in the individual so that the progress of HIV disease is halted. This discussion can then develop so that the students also begin to appreciate that HIV-1 *keeps* re-infecting cells within the

human host.¹³ Thus, by administering anti-HIV-1 drugs, the hope is to not only to destroy viruses, but also to impair the ability of HIV-1 to continue to infect host cells.

3.3 Understanding and evaluating conflicting evidence

It is not unusual for different scientific reports to present conflicting evidence for a given biological mechanism or component. The reasons why results are sometimes conflicting can be explained by the study designs: the results obtained in an experiment can be true within the system that the study uses. Some studies are based on *in vitro* systems, which means that they are reconstitutions of a cellular process done in the test tube. Other studies may be based on cells that carry mutations in important genes. Still other studies may be based on normal cells that have minimal or no alterations, in order to generate a system that reflects the *in vivo* system of a normal cell. The point is that the system used may generate results that are different from those of another system. Therefore, the results may vary, or even be conflicting. Consequently researchers should always examine the methods used by each study in order to make an assessment of the conflicting results in order to make prudent decisions about their own research methodology and strategy.

An area of the HIV-1 life cycle that has had conflicting reports over the years is the integration process. An example of this is the inner-nuclear envelope protein emerin, which has been reported by one research group to be essential for HIV-1 integration whereas another group found that this protein is not required for this process (Jacque *et al.*, 2006; Shun *et al.*, 2007).

A central player in the NHEJ DNA repair pathway is the host protein complex DNA-PK, which is implicated in integration (see section 2.2 above). Over the years DNA-PK has been implicated in a number of different cellular processes such as the p53 response¹⁴ that is part of the DNA damage response pathway, and also as a regulator of transcription of a number of different genes (Bryntesson, 2002, pp. 64–72). I have personal experience of researching DNA-PK. Our research group examined the possible roles of DNA-PK in transcription modulation¹⁵ during DNA

repair and whether DNA-PK is required for the p53 response. Interestingly, the results we obtained were different from other reports. First, we did not find any evidence that DNA-PK is essential for the p53 response following DNA damage (Jimenez *et al.*, 1999). Second, our results also suggested that DNA-PK does not exert an effect on gene transcription during DNA repair (Bryntesson *et al.*, 2001). DNA-PK is therefore a good example of a story that contains conflicting evidence that makes it difficult to determine the exact roles for this protein *in vivo*.

There is also conflicting evidence regarding the requirement for DNA-PK in HIV-1 integration. On the one hand, the results described above suggest that DNA-PK and other NHEJ components are indeed essential for retroviral integration (see section 2.2). But again, there are a couple of reports that present results suggesting that DNA-PK and NHEJ are *not* required for retroviral integration. (Ariumi *et al.*, 2005; Baekelandt *et al.*, 2000). In addition, there are also conflicting reports in the literature regarding the roles of ATM and ATR in the integration process (Arumi *et al.*, 2005; Dehart, *et al.*, 2005; Lau *et al.*, 2005).

It is a very useful exercise for students who are at an advanced level (e.g. in a senior seminar) to examine conflicting scientific reports such as the different reports on retroviral integration mentioned above. Students would be encouraged to critically examine the methods used in these reports and then critique them with the guidance of the instructor. Being able to evaluate scientific reports in this manner is a very important skill to have when entering the research field.

4. NEW CHURCH PRINCIPLES ILLUSTRATED BY THE HIV-1 LIFE CYCLE

4.1 Correspondence

The Writings for the New Church provide us with an opportunity to understand how the natural world corresponds to the spiritual world and to see how closely and inextricably connected they are.¹⁶ We read, “every thing to be found in nature corresponds to something spiritual,” (TCR 201) and further,

nothing at all comes into being in natural creation that does not have a correspondence with the spiritual world . . . Things existing in the natural world are nothing else than effects; their causes, exist in the spiritual world. (AC 5711)

This is a fascinating and unique concept. In the New Church we have the opportunity to supplement our understanding of the natural reality we can observe and test using the scientific method, with the spiritual reality that we believe underpins it all.¹⁷ And the extent to which the spiritual world governs and influences the natural world is far greater than we could ever perceive with our natural eyes:

The whole natural world is responsive to the spiritual world—the natural world not just in general, but in detail. So whatever arises in the natural world out of the spiritual one is called “something that corresponds.” It needs to be realized that the natural world arises from and is sustained in being by the spiritual world, exactly the way an effect relates to its efficient cause. (HH 89)

The Writings contain an extensive glossary of the correspondences of natural phenomena or entities and although every aspect of the natural world is caused by the spiritual, there are many elements such as the HIV-1 life cycle, that are not explained directly by the Writings.¹⁸ In such instances we therefore have to use our knowledge of the Writings and correspondences to the best of our understanding in order to find a possible correspondence.

When we attempt to understand a correspondence that is not directly explained by the Writings, it is very important to acknowledge fully that our conclusions are merely suggestions and that they do not represent the absolute truth. Hopefully, with humility and thorough consultation of the Word, we are able to provide an answer that is close to the truth, but we can never be sure. The following conclusions on the correspondence of the HIV-1 life cycle and its consequences are based on my own interpretations of the Writings for the New Church. I find that these spiritual interpretations help us to understand the natural mechanisms of the virus. I will

examine these interpretations with some specific applications in what follows.

The viral life cycle provides an excellent opportunity to illustrate important New Church principles in the biology classroom. As described above, a patient that has developed AIDS, the final stage of HIV-disease, is susceptible to a variety of infections from different pathogens. The Writings of the New Church tell us that human sicknesses corresponds directly to various aspects of hell: "All who are in hell are the causers of sicknesses . . . for the reason that the hells are steeped in desires and cravings for what is evil" (AC 5713). It makes sense that the hells are responsible for causing disease and sickness. If we accept that our world is truly based on spiritual cause, it is not unreasonable to accept that the hells inflict illness on innocent people.

However, the following passages have a different emphasis:

. . . evil desires and cravings of the lower mind . . . are the origins of those sicknesses, the origins of sicknesses in general being various kinds of intemperance and self-gratification, wholly physical pleasures, as well as feelings of envy, hatred, revenge, lust, and the like, which destroy a person's interiors. (AC 5712)

Moreover every disease corresponds to its own evil; the reason is that everything of man's life is from the spiritual world; and therefore if his spiritual life sickens, evil is derived therefrom into the natural life also, and becomes a disease there. (AC 8364:3)

These passages seem to suggest that the sick person's evil behavior affects their interiors and that their vices are the origins of their sickness. *Arcana Coelestia* 5712 states "the fact that human death is the result of evils or due to sin is well-known in the Church." Swedenborg himself writes of numerous experiences of ailments induced by spirits he was acutely aware of, including stomach ache and tooth ache (AC 5713–5725).

Providing the students with the passages such as the ones quoted above gets their attention and paves the way for an assignment based on the cause and causality of disease from a New Church perspective. It is useful to ask the students to investigate the issues on their own by reading

the passages in the Writings in context and look up articles published in the New Church literature to see what others have concluded about this subject (see Bell, 1996; Bryntesson, 2009; Buss, 1972; Henderson, 1953; Odhner, 1935; Schnarr, 1959 for collateral New Church articles on this topic). A useful quotation to bring to students' attention when discussing this topic is "we may not say now that our sicknesses are an index to specific evils in ourselves [but that diseases] now are rather among the ultimate signs of the general weakness and corruption of the human race as a whole" (Henderson, 1953, 134).

4.2 HIV-1 life cycle correspondences

Disease may have its origin in hell, but the components that make up the human body, created by the Lord, correspond to aspects of heaven. We read: "all parts of the human body correspond to spiritual and celestial things in the Grand Man, which is heaven" and "therefore, heaven is called the Grand Man" (AC 911 and AC 3021). The human body is a representation of Divine order. Disease violates this order.

Just as everything that is in accord with the divine design corresponds to heaven, everything that is contrary to the divine design corresponds to hell. Everything that corresponds to heaven reflects what is good and true, while what corresponds to hell reflects what is evil and false. (HH 113)

Disease, as an expression of falsity and evil and a negation of good and truth, has no place in the Grand Man. Indeed, viruses would have no existence without the host cells that they use to replicate themselves. The HIV-1 life cycle provides very good examples of the violation of the order caused by the virus in a normal healthy cell. A controversial discussion of disease and evil "hooks" the student. Once their affections are engaged, the scene is set for a deeper analysis of the life cycle.

As described in section 2.2 above, the HIV-1 life cycle includes *several* steps that are clearly against the natural order of the living cell. The viral attachment to the host cell, for instance, requires the host cell proteins CD4 and a co-receptor. Although these proteins participate in HIV-1 attach-

ment, they are normally performing other functions in the living cell. Similarly, the viral integration appears to require a range of host proteins that are involved in the DNA damage response pathway and DNA repair. In this process the virus generates a DNA damage that the host proteins recognize and fix. The natural role of these host proteins is to make sure that DNA is maintained so that the cell is not damaged which can jeopardize the well-being of the entire organism by inducing chromosomal instability that can lead to, for example, cancer. Thus the host proteins are functioning like a cellular 911 crew. What the virus does is thus to utilize this cellular emergency response mechanism for its own needs, without contributing to the well being of the cell—in fact, ultimately leading to the host cell's destruction. This is a good example of parasitism and the selfishness of the hells.

The violation of order in the case of HIV-1 integration forces the cell to perform an abnormal function, and the parasite tricks the host cell into a response that ultimately seals the fate of the host cell and the organism. This is an example of how the virus deceives the host cell. It integrates into the host chromosome and in the process, requires the host proteins to come and repair the resultant damage. Although the cell will repair the damage, in the process it will ultimately enable the virus to kill it.

Another example of parasitism by the HIV-1 life cycle is how the viral gp120 protein is modified and processed in the Golgi apparatus of the cell. The host cell, in this instance, treats the viral gp120 protein like a normal host cell protein and modifies it so that it can function in the extracellular space in the body where the HIV-1 virion will be traveling. In this way, it can infect another host cell. Similarly, the hells attempt to use us for their own ends by perverting good. When the virus is using the cell's own functions for its own uses, it is perverting what is good and useful in the body (the Grand Man); it does not benefit the cell, and its motivation is entirely "selfish," a hallmark of the hells.

Another concept that can be discussed in the biology classroom is the relationship between the virus and the immune system¹⁹ as an example of natural selection. As described above, HIV-1 virus evades the immune system continuously because it mutates and thus changes its structure. The virus thus defeats the selective pressure exerted by the immune system. The immune system can be seen as representing the desire for

order because it strives to overcome the disorder generated by the disease-causing pathogens. In this way one can view the interaction between the immune system and pathogens as paralleling the process of temptation. The immune system contains a large number of components (antibodies) that recognize pathogens with high specificity. The first time the immune system encounters a new pathogen the number of components in the immune system that recognize this pathogen are low. However, the immune system will respond to the pathogen and produce more antibodies to the pathogens and ultimately, and often after a period of illness, the pathogen is defeated. Once the immune system has encountered a specific pathogen it remembers it and is capable of mounting a much swifter response to it the second time it is infected by it. It is similar with temptation. In order to be tempted we need to have the truths. Once the hells attack us we can use these truths (antibodies) to fend off the evils. Dr. Norman Berridge points out,

If the response to an invasion of the body is too slow, the invaders multiply and life is threatened. Such is temptation. Later the defenses may gain the upper hand and immunity may be achieved. (Berridge, 1992, 139)

This process is often marked by a “battle” not unlike the illness that is produced when a pathogen is first encountered. Once an evil has been removed to the periphery by means of the process of temptation, the person is better equipped to deal with that particular evil again should it reappear. This parallels the memory that the immune system has for a pathogen once it has encountered it. Berridge also suggests that immunity can be seen as a parallel to the Lord’s glorification on Earth where he conquered and subjugate the hells permanently (Berridge, 1992, 140).

If the immune system is a correspondence to temptation, then the fact that HIV-1 is able to successfully elude the immune system poses an interesting question. What type of temptation is too powerful for an individual to deal with? We know from the Writings of the New Church that no one receives a temptation without having the ability to allow the Lord to defeat it. The parallels between the immune system and temptation make sense when considering pathogens such as rubella (German

measles) that are truly defeated by a healthy immune system. However, HIV-1 not only defeats the immune system—it destroys it, which leads to the death of the individual. Questions like this are useful to pose to the students as they stimulate good discussions in the New Church college biology classroom.

5. CONCLUSIONS

The HIV life cycle is a useful tool for teaching both scientific and spiritual principles in the New Church classroom. A range of biological principles, such as natural selection, drug development and evaluating conflicting scientific evidence, can be illustrated at different course levels ranging from introductory to more in-depth ones. The life cycle of HIV also provides us with excellent opportunities to explore how New Church principles apply to the natural world. The appearance of the syndrome of AIDS has prompted discussions on all levels of life—from personal, to education, to government policy, to global issues. Our New Church understanding of the origins of disease and of the Lord's Providence have a role to play in the debate on all these levels. We all have something to learn from the spiritual implications of the disease. Diseases are often epidemic, but evil is finite and the HIV virus demonstrates its limitations in as much as it ultimately kills its host as well as itself. All hellish tendencies are self-oriented and all selfishness is ultimately unproductive and self-destructive. □

ENDNOTES

1. Recently it was discovered that the statistics of the AIDS epidemic needed modification. The reason was that in some places the estimated number of HIV infections were overestimated. This has now been corrected and the new modified data, included here, was published in December 2007 (UNAIDS, 2007).

2. There are two types of HIV: HIV-1 and HIV-2. The majority of HIV research focuses on HIV-1 since it is much more common than HIV-2. Consequently we have a much better understanding of HIV-1 than HIV-2. Therefore, the focus for this paper is on HIV-1. This section presents the general structure and the life cycle of HIV-1. A full review of our current understanding of the structure and life cycle of HIV-1 would require a large paper, well beyond the scope of this one. Therefore, the descriptions of HIV-1 are simplified here. The main focus for the description of the life cycle is on the early phase with particular emphasis on host DNA repair proteins and DNA damage response components used by the virus to complete the integration step.

3. For general reviews of the structure of HIV-1 see Levy, 2007, pp. 8–12 and Stine 2007, pp. 38–50.

4. The term *virion* refers to the extracellular form of the mature virus. It is this form of HIV-1 that is found in body fluids, e.g. blood.

5. A human cell is defined by its plasma membrane, which surrounds the cell (much like the skin surrounds the human body). A plasma membrane is composed of lipids that form a double layer—known as the lipid bilayer.

6. For reviews of the HIV-1 life cycle see Goff, 2007; Nisole *et al.*, 2004; and Stine, 2007, pp. 41–45.

7. For reviews of the HIV-1 life cycle see Goff, 2007; Nisole *et al.*, 2004; and Stine, 2007, pp. 41–45.

8. Another reason for HIV-1 drug resistance and ability to evade the immune system is that it is able to undergo genetic recombination (i.e. one virus mixes its genome with another virus).

9. *In vitro* literally means “in glass” whereas *in vivo* means “in a living [thing].” The term *in vitro* therefore refers to experiments performed outside a living cell, e.g. in a test tube, whereas *in vivo* refers to studies carried out in, for example, a living cell or a living organism.

10. Evolution occurs when allele (versions of a gene) frequencies change within a population of potentially interbreeding individuals. Note that evolution is different from natural selection. The latter is a mechanism that causes evolution.

11. When someone is given an antibiotic that targets a particular species of bacteria, the antibiotic-sensitive bacteria living in that person succumb. If, however, a sub-population of the species of bacteria that reside in a person is resistant to the antibiotic, then this population survives. Thus the resistant bacteria survive whereas the sensitive bacteria are removed. The resistant bacteria are now able to repopulate the entire environment (the person). In this example, the selective pressure in the environment is the antibiotic. Natural selection takes place because the antibiotic resistant sub-population of the bacteria is able to survive the selective pressure exerted by the antibiotic.

12. No one has yet designed a drug that will remove HIV-1 completely from an infected individual. We would have a cure for HIV-disease when such a drug is developed.

13. The HIV-1 life cycle produces new HIV-1 virions in the infected individual. Some of the new viruses may participate in the infection of another individual. However, many HIV-1 virions will simply infect new host cells within the individual where they were produced. Halting such re-infection would significantly slow down the progression of HIV-disease.

14. The p53 response of the DNA damage response pathway involves the activation of the p53 protein which is involved in cellular responses to DNA damage that includes arresting the cell-cycle or the activation of mechanisms that lead to apoptosis.

15. Transcription is the process by which genes are being expressed. During transcription, a messenger RNA (mRNA) molecule is being synthesized by the protein RNA polymerase. The mRNA, which contains the information stored in the gene in the DNA, is subsequently translated into a protein at the ribosome in the cell. The term “transcription modulation” refers to the regulation of gene transcription. In other words, how gene transcription is turned on and off.

16. By “spiritual world” is meant heaven and hell (AC 5712).

17. It is essential to keep in mind that science and religion are two fundamentally different approaches to answer questions about reality. Science concerns itself with the natural world only, by means of the scientific method. Science is incapable of addressing questions pertaining to the spiritual aspects of reality. Dr. Grant Doering expresses this well: “a scientist fails in his

function when he states a final cause; fails, that is, as a scientist, not as a human being. He errs as much when, or if, he denies that there can be a primary or final cause. What I am saying here is that science does not properly deal with final causes; that is not its job. Science is concerned about secondary causes. Philosophers may deal with final cause, but in fact final cause is what religion is all about" (Doering, 1968). It is therefore very important to make it clear to students in a New Church classroom when we discuss a New Church perspective of biological phenomena that we are no longer talking about science proper, but are rather in the realm of theology.

18. One reason for why some natural phenomena are not explained in the Writings is that they were discovered after the Writings were written.

19. An interesting and fascinating interpretation of what the immune system may correspond to can be seen in Dr. Norman Berridge's book *The Natural Basis of Spiritual Reality*.

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