Christian Spirituality and Science

Issues in the Contemporary World

Volume 9
Issue 1 *Subjective Reality, Complexity and Programmed Cell Death*
Article 3

2013

Genetically Programmed Cell Death: Concepts of Death and Immortality in the Age of the Genome

Paul U. Cameron
Monash University, paul.u.cameron@monash.edu

Lynden Rogers
Avondale College of Higher Education, lynden.rogers@avondale.edu.au

Genetically Programmed Cell Death: Concepts of Death and Immortality in the Age of the Genome.

Associate Professor Paul U Cameron,
Clinical Immunologist and Immunopathologist
Infectious Diseases Department, Monash University
Pathology Department, Alfred Hospital
Infectious Diseases Unit, Alfred Hospital
Melbourne, Victoria

and

Lynden J Rogers
School of Science and Mathematics
Avondale College of Higher Education
Cooranbong, NSW

ABSTRACT

Scientific discoveries have done much to complicate matters of life and death. Perhaps the most significant such revelation in recent decades has been that every cell in our bodies has a built-in, and genetically controlled suicide capability. This is also true of most other organisms. Cells know how to die! It has been discovered that programmed cell death turns out to be vitally important in many life processes such as: the development of the mature organism from a single cell, combatting foreign threats, such as infections, and controlling rampant cell growth, as found in various cancers. It is also important in the normal regeneration of skin and gut lining. Cell death appears to be much more inextricably intertwined with life than may have been earlier supposed. This paper introduces this discussion and explores some of the implications of programmed cell death for a Christian understanding of the relationship between life and death.

Keywords: necrosis, programmed cell death, apoptosis, immunity

1. INTRODUCTION

One of the dominant motifs woven through the Judeo-Christian world view is that of death as the ultimate expression of evil, a foe that must and will be overcome.[1] From the Genesis account of the fall and the expulsion from Eden[2] through to the Revelation account of a new world where death and sorrow are no more, there is an underlying concept of death as an enemy from which humans can be saved.[3] Indeed, one of the best known verses in the canon, John 3:16, encapsulates this view.[4] Furthermore, many Christians understand not just human death but death in any form and under all circumstances, to be a result

of sin's "curse". However, it may be asked how well this view of death as the ultimate enemy accords with the observations of modern biology.

2. ISSUES OF LIFE AND DEATH

There is considerable evidence to suggest that the idea of death in biblical times was very simple and was associated only with the world of animals and humans. Animals were either "quick" (moving) or "dead", as in Acts 10:42[5]. Certainly, life and death were holistic in that these states applied to the whole organism at once. Texts such as Gen 9:4, Lev 17:13, 14 and Deut 12:23[6] suggest also that, for the Hebrews, life was closely associated with blood. Indeed, the whole sanctuary ritual reflected this understanding. This may suggest that only animals with blood were regarded as being alive. Interestingly, some evidence suggests that plants, being stationary in any case, were not thought of as being alive or dead in the same way as were animals; they were either "green" or "dry".[7] Clearly, such an understanding would have allowed the animals and humans in the Garden of Eden, all of which according to the literal reading of the text were vegetarian, to eat without causing death. That such ingestion and digestion may have involved the systematic elimination of microorganisms within the gut represented no problem since all such processes were invisible to those in Bible times. Similarly, with no concept of the "cell", they would not have been theologically challenged by the realisation that the outer layers of skin, for example, are comprised of dead cells.

All this has changed. Biological science has revealed that all living organisms, both plants and animals, are composed of small basic units called cells. These work in similar ways in plants and animals and are fundamental to all processes of life and death for both. We also now recognise the existence of a huge host of microorganisms. Some of these are beneficial, even essential, to higher life forms while others are deadly. Furthermore, we understand that living entities utilise many dead cells, such as those found in the outer layer of skin, in their quest for survival, and continually produce them. So in this sense even living things are not completely "alive". Of course, science still has much to learn about life and death. Viruses provide an illustration of the difficulty of actually defining life. Although possessing a small amount of either DNA or RNA contained within a protein coat, they do not have any intrinsic metabolism and replicate only inside the cells of other organisms. For these reasons they are not regarded as actually being "alive". Additionally, Australia has many fascinating life forms, such as cryptobiotic midge larvae, which can lie dormant and desiccated for years under dry outback river beds, to all intents and purposes dead and showing no visible sign of metabolism. Yet a sudden, soaking rain can "wake" them up, whereupon they quickly become active

and reproduce, all in the few days the puddles remain.[8] Just what differentiates such an organism in a quiescent state from one which is actually dead is not well understood at all. Such discoveries have enormously complicated our comprehension of death.

One breakthrough which has proved central to an understanding of many areas of cell biology, including reproduction and immunology, concerns the *programmed* death of cells. There is now an explosion of scientific literature on this topic. A milestone in this understanding was marked by the awarding of the Nobel Prize in medicine in 2002 to John Sulston, Sydney Brenner and Robert Horvitz for their work on the genetic control of cell development and death.[9] What exactly did these scientists do and why did their discoveries merit such recognition? What is programmed cell death and why is it so significant? What is the relationship between death at the single cellular level and the death of an organism? Finally, what are the implications of the existence of such a biological system for our reading of the Genesis account, particularly concerning the effect of early human history on death throughout the biosphere? This paper addresses these questions. First, we need to differentiate between two main types of cell death.

3. NECROSIS AND APOPTOSIS: DIFFERENT TYPES OF CELL DEATH

Living organisms are found within a relatively broad range of environments or ecological niches, yet each is quite restricted in the range of conditions it can tolerate.[10] Mammals, although successful in populating various hostile environments because of their ability to generate body heat and their utilisation of various forms of insulation, have cellular building blocks which are particularly limited in this regard. Isolated mammalian cells are very fragile compared to, for example, bacteria, and can only exist momentarily outside the body. Also, they die very easily if exposed to low temperatures, as evidenced by the death of the fingers, toes or other extremities because of frostbite. Exposure to high temperature is similarly damaging. Small children can suffer severe consequences from high fevers, while a rise in body temperature of as little as 5 degrees C can produce heat stroke and death in hot, dry, desert environments. Many bear the scars of encounters with hot objects such as boiling water, stove hotplates or fires. These result from the violent death of individual cells making up the affected tissue.

Such cell death results not only from physical damage but also from metabolic insults such as exposure to carbon monoxide (from car exhausts), cyanide, or the loss of nutrients – oxygen, glucose, essential amino acids, protein components and vitamins. From whatever cause it may arise, this traumatic form of cell death is called "necrosis" (Greek *necros*, meaning "dead body").

But over the last 30 years biologists

have become aware of another, more deliberate, mechanism of cell death, one quite distinct from necrosis. This is programmed cell death. John Kerr, an Australian pathologist whose interest was in cancer research, and his associates were the first to coin a term designating this process in pathological specimens.[11] He suggested the term "apoptosis" (Greek *apoptosis*, meaning "falling off"). The simplest way to demonstrate cell death by this means is to deprive cells in culture medium of the blood serum that is normally added to maintain cell growth. This was, in fact, the way it was first observed experimentally. The process of apoptosis is in effect a systematic suicide of the cell according to a genetically pre-programmed path.

One of the earliest markers of apoptosis is a characteristic change in the nucleus which contains the governing genetic material of the cell, the DNA. The DNA is associated with proteins called histones, which produce structures called nucleosomes. Each nucleosome protects a DNA span of some 180-200 nucleotide bases, so that there is a small gap of "naked" DNA every 200 or so bases. It was soon discovered that in apoptosis a DNase enzyme cuts the unprotected DNA between the nucleosomes, producing a DNA "ladder" made up of multiples of these 200 or so bases. This DNase activity was clearly due to some other cell enzyme produced by the cell itself and was obviously internally, i.e. genetically, controlled. This process of apoptosis may be seen under a microscope as a ruffling of the cell membrane which proceeds to clumping or condensation of the cell nucleus and eventually to the development of a featureless cell cytoplasm with dense fragments of nuclei.

This nuclear fragmentation gave rise to one of the first instrumental tests for identifying the process of apoptosis. The method initially involved extracting DNA from a cell thought to be dying by apoptosis and separating it according to size by running it on an electrophoretic gel in order to allow the size of DNA segments to be determined. If this produced a "ladder" of DNA fragments with multiples of 180-200 bases then apoptosis was confirmed. More modern methods use sophisticated measures that detect the actual ends of the DNA fragments, the number of which is greatly increased due to the breaking up of the DNA during apoptosis. These sensitive techniques enable the identification of apoptosis in individual cells. The nuclear fragmentation is eventually followed (generally some hours later) by modifications to the cell surface which allow the apoptotic cells to be recognised by phagocytic cells (cells which engulf dead or harmful cells and organisms), leading to their ingestion and complete destruction.

While apoptosis was the first form of programmed cell death to be identified by microscopy, and has been well-characterised biochemically, other forms of programmed cell death are

also now known to exist.[12] It is now clearly understood that the mechanisms controlling programmed cell death are genetically controlled and are "built in" to life forms at a very fundamental level. The award of the 2002 Nobel Prize to Sulston, Brenner and Horvitz was a recognition of their important roles in providing vital insights into these processes.

It was rapidly appreciated that the process of apoptosis is vital to normal embryological development and of critical importance to the immune system. It also proved to be important in curbing abnormal cell growth, as in the case of cancers. Related processes of programmed cell death have also been found to be important in regulating the normal processes of renewal in many tissues, including the skin and gut. Sections 4–7 of this paper describe the role of programmed cell death in these significant life processes.

4. PROGRAMMED CELL DEATH IN EMBRYOLOGICAL DEVELOPMENT

All multicellular organisms develop from a single cell, a fertilised ovum. The embryo advances from a single cell to a cluster of cells (morula), next to a ball of cells with a central cavity (blastocyst), then to a plate of cells which eventually develops into the layers of cells (gastrula) that progressively differentiate to form a head and a tail end. This then folds to produce a spinal cord. In each of these steps there must be remodelling of the structure of the cell cluster, not only by a process of controlled cell proliferation but one of regulated cell loss. From the formation of the cavity in the blastocyst onwards, apoptosis has been found to be critical in this moulding process. For example, in a developing human embryo, "between the forty-sixth and fifty second days in the womb the interdigital webbing of the hand suddenly disappears, leaving behind five beautifully shaped fingers."[13]

Another instance that demonstrates the fundamental importance of programmed cell death in embryology concerns human brain development. During the second trimester there is huge proliferation of neurons within the cerebral cortex. About half of these are subplate neurons, a special category which form some of the first functional cortical brain circuits. They function in some sense as neural "scaffolding", and provide crucial regulation of cortical development and plasticity. During the third trimester and early post-natal life most of these subplate neurons die by apoptosis, their essential work done.[14] It is possible that a failure of these apoptotic regulatory mechanisms may be associated with some forms of autism.[15]

5. APOPTOSIS IN THE IMMUNE SYSTEM

One of the most important survival mechanisms for multicellular organisms is the discrimination between self, harmless variations of self and nonself. A further task is to differen-

tiate non-self organisms which do not pose any particular threat, such as food components, from those which may threaten survival. The immune system is the body's defence barrier that makes these decisions and determines an appropriate response.

The development of genetically programmed mechanisms for cell death provides a number of "hooks" into which the immune system can link in order to kill foreign, abnormal or virus-infected cells. It has been found that the immune responses in multicellular organisms comprise a number of tiered layers. Simple organisms exhibit only the lower, "innate" levels, whereas more advanced life forms, such as mammals, whilst retaining the more simple mechanisms, also utilise a range of "adaptive" mechanisms. These are much more sophisticated and effective. It should be noted at this point that although the term "immune" most correctly relates only to the consequences of these adaptive mechanisms, the terms "immune system" and "immune response" are frequently, and somewhat loosely, used to describe all functions within the body's defence system. However, in this brief treatment we consider only adaptive immunity. Not surprisingly, the complex signalling pathways and processes found within the human immune system have been particularly well defined.

Adaptive immunity involves the system's ability to recall a previous encounter with a foreign organism or cell and to respond rapidly and effectively on subsequent exposure. The increased efficiencies of such an immune system have contributed to the success of mammals in a wide range of environments and in particular to their ability to colonise new environments rapidly where novel parasites and microbes pose a threat. Without adaptive immunity, protection from a pathogen requires changes in the genetic repertoire. Since genome changes can only occur as a result of differential survival such genetic shifts are slow and may require many generations. On the other hand, adaptive immunity, with its memory of previous exposures to harmful organisms, allows survival and thus the colonisation of a new environment within a single generation.

It was Peter Medawar who recognised that lymphocytes (small white blood cells) were responsible for this memory. In 1960 he and Macfarlane Burnett received the Nobel Prize for their description of tolerance and immune recognition and their identification of clonal selection of lymphocytes as the basis of immunological memory.[16] (Before their observations were published it was thought that these cells were somehow "instructed" to respond to foreign material only after exposure to that material.) However, although the existence of immunological memory and tolerance was established by the 1960s, the basis for such recognition was not established until much later.

It was soon realised that these defence mechanisms could be activated by organ transplants. In fact, one of the earliest recognised examples of this phenomenon was graft rejection. It was noted that if skin from one mouse was grafted onto a genetically different mouse it would be rejected, generally after a delay of some days. If a second graft from the same donor was applied some time later it would be rejected within minutes or hours. However, if the second graft was from a new donor the rate of the rejection process was no different from the first graft. Thus the memory for graft exposure is specific for each donor. The number of reacting cells is increased during exposure to a graft and when reexposed to a graft from the same source this large population of reactive cells recognises the foreign proteins and rejects them rapidly.

The characterisation of the action of lymphocytes acting in the immune response of graft rejection has now led to the recognition of several different subgroups within these lymphocytes, all contributing to a complex interaction that leads to adaptive immunity and memory. There are three stages to the process of protection through adaptive immunity: controlled genetic recombination; clonal selection of those cells that show reactivity to the foreign material; and the subsequent elimination of the threat. Both of the last two stages involve apoptosis.

Controlled Genetic Recombination

The human genome contains only about 20,000 - 25,000 different protein coding genes. These genes must code for embryonic development as well as many details concerning cell and tissue function for the life of the organism. Even without these additional (and most important!) functions there is no possibility that such a small number of genes could individually code for protection against not only pathogens but each of the almost infinite number of possible antigen configurations which might pose a threat. So how does the immune system prepare itself to counter all such eventualities?

The answer to this dilemma is found in the process of controlled genetic recombination, which involves the generation of lymphocytes with receptors which have a wide range of recognition specificity from which selection can be made. This occurs within two parallel systems. For T lymphocytes (T cells), it takes place in the thymus, a small organ of the immune system which is located behind the sternum near the heart. For B lymphocytes (B cells) this occurs in the bone marrow. These cells have similar genetic coding mechanisms that provide for the generation of a huge amount of variation in surface receptors. These include recombination from multiple small genes and then the introduction of diversity by a random joining event which produces a bewildering array of "fixes", mostly to problems which will never be encountered! It transpires that

a small animal, such as a tadpole, having as few as one million lymphocytes, can generate an immune response to virtually any protein to which it might be exposed, although in an animal of this size there may only be one cell in the whole body that can recognise the foreign material. Thus, vertebrates are considered to have essentially an unlimited repertoire or ability to respond to foreign proteins.

Clonal Selection

Some cells generated by this process of genetic modification turn out to be "self reactive", i.e. reactive to the host organism. If they were allowed to circulate they could destroy huge numbers of perfectly functional cells, thus creating havoc. This does in fact happen in the case of certain autoimmune diseases. Such cells must be quickly eliminated and are, in fact, removed by apoptosis.

Once launched on their defensive career the remaining randomly specific lymphocytes need the stimulus of a "recognition" event in order to survive. As earlier noted, for a very large majority of them this never occurs. After a time all such cells die by apoptotic suicide.

However, for some lymphocytes a recognition event will occur. This recognition is mediated by molecules on the surface of the lymphocytes which are the products of the rearranged genes. On T cells these are T cell receptors and on B cells they are B cell receptors. Both killer T cell (cytotoxic T cells) and helper T cell responses use the same T cell receptors. For B cells a variant form of the secreted antibody or immunoglobulin produced by that cell is used as a receptor on the cell surface.

When such recognition occurs the next stage, for both T and B cells, involves the selective replication of those cells that interact most strongly with the foreign protein. Thus this cell proliferation is highly specific for the foreign protein or antigen. This expansion of cells takes place by clonal selection over 5 to7 days, during which there may have been 8 to10 cycles of doubling[17]. The expanded population of cells, however, is long-lived so that when the foreign material is encountered again there are enough cells to respond immediately, thus eliminating the threat. In this sense the expanded clonal cell line provides "memory" of that specific antigen and the animal is said to be "immune".

Elimination of the Threat by Apoptosis

The cells killing the organ transplant, or other outside "threat" as the case may be, do so first by recognising the cells as foreign and then, fast on the draw, delivering a killing signal to the foreign cell which initiates programmed cell suicide. The cell under attack has no defence, and will die.

6. APOPTOSIS AND CANCERS

Cancer is an unregulated expansion of cells. This is usually initiated by mutations in genes that control cell

growth, lifespan or death, i.e. so-called "cancer genes". Normally, damage to a cell by: carcinogens typically found in tobacco smoke, UV light, isotopic particles or gamma radiation consists of altered nucleotide bases in one strand of the cellular DNA. However, there are two such strands and a number of mechanisms exist for repairing breaks or modifications in one of these. If these strategies cannot restore the original form then permanent damage is caused. These changes to the DNA code may result in the production of abnormal proteins and hence altered cell growth. Cells which accumulate too much damage to the DNA may enter the apoptotic path and politely destroy themselves for the good of the organism. However, this does not always occur.

The genes that are mutated in cancer cells and which result in increased growth include oncogenes, a particular sub-population of genes that normally regulate cell growth but can be altered, allowing accelerated or uncontrolled cell growth. Some gene abnormalities are associated with loss of the normal process of apoptotic cell death so that the cells proliferate without death and thus become immortal. This was the case for Henrietta Lacks, cells from whose cancerous tumour famously became one of the most heavily used cell lines in the biological research world. According to convention these cells are identified by the first two letters of the donor's given name and family name and so are known as "HeLa" cells.[18] Usually a cell will accumulate mutations in several such genes before malignancy becomes evident.

Thus cancers can result from changes in a number of cancer genes, which direct and control apoptosis. Cancer genes can be categorized into several groups: tumour suppressor genes, genes that produce growth factors, DNA repair enzymes and genes involved in apoptotic pathways. Clearly, if there is a loss of these regulatory mechanisms then any irregular cell growth may proceed unchecked. In fact, the study of the genetics of cancer has been one of the main areas showing the important role of apoptosis in the regulation of cell numbers and cell growth and thus of apoptosis as a target for drug therapy.

7. PROGRAMMED CELL DEATH IN NORMAL SKIN AND GUT

As noted earlier, unprotected cells are physically fragile and if exposed to the environment will rapidly die. Cells need to be kept within a temperature range of about 30 to 40 °C and kept moist in a solution with nutrients and defined salts. Cells kept in fresh water will swell by osmosis until they disintegrate. Conversely, if immersed in sea water they will shrink, also by osmosis, and die. Some sort of covering is needed to protect cells in most multicellular organisms. Crustaceans have a carapace, a hard external shell to protect the animal from the external environment, while land molluscs

produce secretions (slime) that insulate them from their environment. Mammals have a system of physical protection based on skin and growths from this skin (hair or wool).

The outermost layer of skin is a beautifully crafted system composed of dead cells which can cope with the environmental insults to which they are frequently exposed. These dead cells are continually lost by abrasion and must be replaced. They do so by continual cell division in the bottom layer of the skin. These cells then accumulate a substance, keratin, within each cell and eventually undergo a form of sequential, programmed cell death called "cornification". In this situation the complete destruction and elimination of the cells, as in apoptosis, is not desirable, since they are required as a barrier.[19] A similar mechanism operates in the bladder, mouth and throat.

In the gut the mechanism is somewhat similar but there the lining consists of a single layer of cells rather than stacked layers. Growth and proliferation occurs in the crypts, glands located at the bottom of and between the villi, which are the small projections into the food flow within the gut. The lining cells produced in the crypts gradually migrate up to the tips of the villi where their numbers are controlled by programmed cell death mechanisms and abrasive loss into the gut. In this way there is continual renewal of the cells lining the gut as they are worn away by passing food.

In all of these systems cells damaged by environmental insults are lost and replaced without causing damage to the organism. Problems occur when there is significant damage to the proliferating cells in the basal layers. For example, genetic forms of bowel cancers result from abnormalities of genes that control either the proliferation or programmed death of these gut-lining cells.

8. SUMMARY OF CURRENT UNDERSTANDING OF PROGRAMMED CELL DEATH

A number of conclusions can be made. These include the following key points.

- There is a complex system composed of many genes which program cell death mechanisms.
- Programmed cell death pathways exist in all organisms from yeast to man.
- Without programmed cell death the normal embryological development of an organism from a single cell, the fertilised ovum, into a mature adult could not occur.
- Apoptosis is critically important in the development of the immune system. Without it the adaptive immune response and immunological memory could not exist.
- The removal of cells by apoptosis is vital to the protection of the organism from

the development of tumours and cancers that might otherwise result in its death.

- Programmed cell death mechanisms are involved in the normal development and maintenance of skin and gut lining.

9. THE RELATIONSHIP BETWEEN CELL DEATH AND THE DEATH OF THE ORGANISM

The life of an organism is a consequence of, and is evidenced by, the continuation of a number of activities and processes carried out at the cellular level. Furthermore, there are a number of vital body systems in which the malfunction or death of key cells brings about rapid, even instant death of the organism as a whole. In this sense life on Earth, even in its highest human dimensions of sentience, consciousness and awareness of the spiritual, is ultimately dependent on the successful continuity of cellular processes. Of course, while the demise of these key cells brings death to the organism other cells can die with little or no ill effect, sometimes even with benefit. In fact, as has been shown, mechanisms of programmed cell death contribute for the most part to the normal development and *survival* of the organism as a whole. One might ask whether there is any moral difference between the programmed death of a useless or dangerous cell, or the incidental death of a vital cell. Does the significance of a cell's death depend on whether or not its death benefits or harms, even kills, the organism as a whole? This question subtly undergirds any modern discussion of the morality of life and death.

One might also ask whether the cessation of life processes in a cell can be regarded as being of the same moral significance as the death of the organism as a whole. At a reductionist level the answer is probably "yes". However, at the holistic level, where the whole is regarded as more than simply the sum of the parts, the life of a sophisticated organism may be regarded as a higher entity, emergent from continuing cellular processes, but morally differentiable from the "life" possessed by the constituent cells. In this case the answer may well be "no". However, even in the latter case some modifications may be required to the traditional Christian understanding of life and death processes operative in "the beginning". Certainly, the way this question is answered might influence the comparative appeal of the models discussed below.

10. IMPLICATIONS FOR CHRISTIAN THOUGHT

10.1 The Origin of Programmed Cell Death Mechanisms

The complex genetic system[20] controlling programmed cell death comprises hundreds of the estimated 20,000 – 25,000 genes present in the human genome[21] and is similarly represented in all lower species. These cell death

processes are present from life's beginning to its end. Death at this level appears to be an essential part of life! Although not the subject of this paper, we also know that the same is true at the level of ecological systems.[22] All growth and proliferation is balanced by death and decay. This dependence of life on death allows stable systems to exist, dependent only on energy input from the Sun. From a purely scientific perspective it is difficult to conceive of life without death. This raises some obvious theological issues for Christians.

Modern Christians face two main possibilities for the origin of the programming which controls life and death at the cellular level. Either the sophisticated genetic system currently controlling cell death in all species was created by divine fiat (creationist model) or it has evolved stepwise in response to the requirements for cell survival during the gradual development of organisms from simple to complex (evolutionary model). These contrasting scenarios are explored below, with a particular focus on creationist models.

10.2 Creationist Models

For creationists two main possibilities stand out. What might be called the "pre-fall" model suggests that all these mechanisms must have been present as part of the original creation before the fall. However, according to the "post-fall" model all mechanisms for programmed cell death must have been introduced by God after the fall. It may also be possible to construct intermediate models between these extremes. We will refer to these as "mixed" models.

Pre-Fall Model

This model assumes that the original creation did indeed incorporate all the genetic machinery governing programmed cell death and that not only embryological development but immune responses and protection from malignancy occurred in the pre-human-fall created order. It would also seem most consistent to posit the processes of cell death and the consequent death of larger organisms as being essential aspects of this order. In other words, life for most of the creation then was very much like life now. Under this scenario mankind would have been the only creature for which immortality was possible, this being a "higher-level state" imposed on the natural order by the "Tree of Life". Once mankind fell and was excluded from this tree then the natural order governed humanity, just as it had all life outside the garden. As far as the authors are aware, only one Adventist author has described a model anything like this.[23]

The pre-fall model is clearly successful in some respects.

- The proposed picture of cell death and the death of higher organisms would enable the existence "in the beginning" of stable ecosystems, waste

recycling and population limits, all of which are very consistent with the findings of modern science.

- It also provides an obvious role for the Tree of Life, namely the inhibition of the natural order of death and recycling for mankind. Indeed, the most obvious reading of Gen 3:22 is that prolonged life for humanity was dependent upon eating from the Tree of Life. This model also makes it easy to understand why access to it was forbidden after the fall.
- It may also be understood to be in harmony with other aspects of a literal reading of Genesis. The context of Genesis 1 & 2 can be understood to imply the creation of a special garden, outside of which is a natural order in need of "subduing"[24]. Perhaps the fact that, according to the narrative, Adam was not created in the Garden but later brought into it,[25] may also indicate that Adam did not have intrinsic eternal life and that he would need a Tree of Life.
- It may also be consistent with those biblical statements in which God appears to be comparatively unconcerned with the death of animals, or with predation.[26]
- It is entirely consistent with all known functions of cell death.

It also suffers from some significant failures.

- Most obviously and importantly it does not accord with the traditional paradigms of universal perfection and eternal life which many Christians understand to be associated with both the beginning and end of human history according to a variety of scriptural passages.[27]
- It may be difficult to reconcile a God whose original fiat creation included such features as programmed cell death with the character of Christ, who claimed to be the "resurrection and the life" incarnate.

Post-fall Model

This model assumes that the initial creation was entirely free from any death or decay. This model is often portrayed in conservative Christian literature. According to this view all life came forth perfect and immortal, albeit conditionally, from the Creator's hands and there could have been no death or decay at any level of life's hierarchy before the fall. Accordingly, all programmed cell death mechanisms would have been established by God in a post-fall creation "recall", in order to assist the maturation and survival of organisms now facing the many deadly environmental insults brought about by man's fall. This "re-creative" work must have taken place over a short time, perhaps again by divine

fiat, since there is insufficient time in traditional Christian time scales to allow sequential development. In any case, most Christians taking this view understand the Genesis account to be describing a sudden rather than a gradual transformation of nature. According to this view, mechanisms of programmed cell death would be seen essentially as the curse of man's sin being visited upon creation at large.

Although not within any awareness of programmed cell death as such, historical Adventism could be said to have identified most strongly with this model. Despite the dissemination of knowledge concerning programmed cell death over recent decades the writers are unaware of any serious Adventist attempt to integrate these data into the "all death post-fall" traditional view. This model has been assumed rather than defended by most modern Adventist writers on Origins.

This view is again successful in many respects.

- Since the cause of all death is identified as Satan, sin and the fall of man, God's character is exonerated from any first-cause responsibility for death in any form.
- Clearly, too, this view is compatible with at least the immunological function of programmed cell death since the "fallen" world could be expected to contain many threatening organisms, against which defence would be required.

However, it also suffers from some shortcomings.

- Since programmed cell death appears to be inextricably implicated in the embryological development of all new life, it is difficult to understand how new generations could have arisen in pre-fall Eden. Yet those supporting this model recognise that God clearly bade his "perfect" creation be fruitful.
- Further, it appears somewhat ironic that mechanisms of programmed cell *death* should have been employed in the promulgation of *life*: the embryological development of new life and with the protection of that life from environmental insult.
- Another problem arises from the perception of some adherents that pre-fall flowers may have been everlasting. Ellen White wrote that the Earth as it came from the Creator's hand "bore no blight of decay or shadow of the curse".[28] Also suggestive of the same sentiment is her description of the scene immediately post-fall: "As they witnessed in drooping flower and falling leaf the first signs of decay, Adam and his companion mourned . . . The death of the frail, delicate

flowers was indeed a cause for sorrow; but when the goodly trees cast off their leaves, the scene brought vividly to mind the stern fact that death is the portion of every living thing."[29] Since seeds today cannot form or germinate without the programmed death of the cells comprising the flower it is difficult to understand how pre-fall plant reproduction occurred at all. If it did, it must have been by mechanisms very different from those currently operating.

- This view also struggles to understand the function of the Tree of Life. The context suggests that the Tree of Life existed only for humans, since no mention is made of its intended consumption by animals. Why make it available just to humans? Further, if both animals and humans were intrinsically free of death processes what purpose was served by having this tree at all? Some have conjectured that humans alone may have been created without intrinsic immortality and that this would have been "awarded" by God after a suitable period of obedience,[30] whereupon the tree may have been redundant and would, perhaps, have been withdrawn. The Bible, however, is silent on this point. Perhaps, too, the Tree may have simply been a visible metaphor of eternal life, as it is presumably in the New Earth.[31] However, such an interpretation goes somewhat against a literal reading of the text.
- Pre-fall life must have operated according to fundamentally different microbiological principles and mechanisms and therefore the post-fall modifications required to build in and manage mortality must have been fundamental and extensive. Yet changes on such a scale are not obvious from the description of this process in scripture.

Mixed Models

It is clearly possible to construct hybrids of the Post-fall and Pre-fall models described above. For example, programmed cell death processes may have been part of the original creation but were intended simply to assist in embryological development, good digestion and insulation from the environment, benign and congenial as it was. Without any embarrassment such a composite model might also recognise as inevitable the programmed death of plant cells and the drooping of flowers in the process of fruit and grain maturation. Such instances of cell death would not be seen as a result or manifestation of evil but simply as the sensible and sustainable way in which God chose to build His "perfect" and fully functional world. Such models

would draw a clear distinction between death at the cellular level and the death of a higher organism, particularly a conscious, sentient, death-aware organism such as a human being!

According to these mixed models, programmed cell death mechanisms might have been adapted by God after the fall and utilised to meet the emergent threats, such as pathogens and runaway cell proliferation, which were somehow induced by man's fall.

Although not specifically discussing programmed cell death, Leonard Brand is one of the few Adventist scientists who has addressed some of these issues. Essentially he presented some mixed models for discussion, exploring various aspects of pre-fall death. Brand touched on the vexed issue of apple cores in Eden, taking the view that it "does not seem reasonable to suggest that they accumulated and lasted forever." He also noted that the fruits which comprised part of the original diet begin as flowers and become edible only after the flower petals die. A similar picture, he pointed out, emerges with grains. Brand also referred to the dung beetle, a species whose whole life cycle appears to be designed around recycling. Although Brand did not commit to any one position he suggested that a variety of views are compatible with scripture, including one which acknowledges the pre-fall existence of the death of plant cells, the generation of some waste products and some recycling of this waste – presumably by the likes of bacteria and dung beetles doing pretty much what they do today. He suggested that, according to such a view, White's comments concerning the post-fall decay might refer principally to the "loss of strength, soundness, health and beauty" rather than to the death of plant cells, including those of flowers.[32]

Such composite models achieve some resolutions.

- They still identify the death of higher organisms as a consequence of Satan, evil and the fall of humankind. Thus it might be claimed that they are consistent with such scriptures as Rom 5:12-19 and Rom 8:22.
- They may be said to reflect God's omniscience. Perhaps an all-knowing God who could foresee man's fall might be expected providently to build in mechanisms which could be adapted for dealing with this contingency when it occurred.
- These views are entirely compatible with all the known functions and instances of cell death, not just those related to the immune system, as in the Post-fall model. They are not embarrassed by apoptosis in embryological development, in cell death processes within the skin and gut, or by the death of flowers occasioned by the

production of Edenic fruit.

They also suffer from some inadequacies.

- In admitting that programmed cell death was part of the original creation it could be argued that adherents of composite views have fundamentally compromised on this question and commenced travel on a "slippery slope" which can only end in attribution of all death to God Himself.
- Such views are also faced with the serious challenge of deciding at what level in the hierarchy of organisms death becomes attributable to "sin" and hence morally "bad".
- They also struggle to adequately understand the function of the Tree of Life, for similar reasons to those outlined under the Post-fall model.
- Those committed to a high view of the prophetic authority of Ellen White may understandably argue that such views are in clear opposition to the picture which emerges from her pen in so many places.

10.3 Evolutionary Models for the Origin of Programmed Cell Death

Theistic evolutionary models suppose that God either instigated or allowed the gradual development of life over a much longer period than that usually associated with fiat creation. Evolutionary views have not found many adherents among literalist readers of scripture. Within this context most Seventh-day Adventists authors have clearly distanced themselves from such positions[33], although there have been some exceptions.[34] Certainly, some evolutionary version is accepted by other conservative Christians and very widely so throughout Christianity at large.[35] Accordingly, it is appropriate also to critique this view in the context of the creationist models with respect to the consistency of the manner in which it contextualises and explains programmed cell death.

Adherents of theistic evolution would regard such models as being successful in explaining significant features of cell death. These successes are mainly in the scientific area.

- The presence of simple cell death mechanisms in quite primitive organisms, with a gradual diversification and increase in complexity apparent as one approaches the higher taxonomic levels, is consistent with prevailing evolutionary views suggesting that mechanisms controlling cell death appeared early in cellular evolution, both within single-celled prokaryotes (cells lacking a membrane-bound nucleus) and during the development of eukaryotic (cells with a membrane-bound nucleus)

multicellular organisms. Once it occurred as a vital part of defence it became part of the larger evolutionary process in multicellular organisms, and subsequently proliferated.[36]

- The presence in eukaryotic cells of genetically independent mitochondria may not represent the optimal design one might expect in terms of a creation model. Evidence suggests that the latter became intracellular symbionts very early in eukaryotic evolution[37]. It is also true that once this took place the significant interactions between mitochondria and the rest of the cellular structure, with their nuclear genetic dependencies, would have dramatically increased the possibilities for adaptive mechanisms such as apoptosis and other forms of programmed cell death.

Additional successes may be suggested by the arguable survival advantage of organisms that have incorporated mechanisms of programmed cell death.

- In the case of prokaryotic organisms mechanisms of programmed cell death in the circumstance of limited nutrients would allow for rapid adaptation of the population of organisms by maximising nutrients to those most adapted to utilising them.[38] Individual suicide of "stressed"' cells provides maximal probability for the survival of the fittest as regards the population as a corporate whole, which could be expected to promote rapid genetic evolution of the species. Recycling of nutrients from apoptotic cells would also maximise energy efficiency and thus contribute to the health of the overall colony.
- The continued development of colonial and multicellular organisms is favoured by mechanisms of programmed cell death. This is so both for protection via phagocytosis and in moulding the colony, in the same way as embryological development is dependent on apoptosis.
- The evolution of immunity both in its primitive innate form and in more adaptive forms requires apoptosis to allow for clonal selection, an instance of natural selection at the cellular level.

This model presents significant problems for many conservative Christians, mostly at the theological level.

- The acceptance of any evolutionary model for the origin of life implies a long history for life and most likely for man as well. Such a chronology is seen by many Christians as incompatible with the biblical account.
- Natural selection implies a long

history of ecological systems involving differential survival and death or at least differential fertility in the presence of mortality. Such a picture of "nature red in tooth and claw", prior to any possibility of a human fall and over such long periods, is again seen by many Christians as incompatible with both the creation story and the biblical picture of God.

- According to this model it is clear that immortality for humans can only result from a superposition on the natural order by God or a total reconstruction by Him of that order.

11. CONCLUSION

It is clear that none of the models outlined are without problems. This might be expected whenever finite human minds attempt to probe events deep "in the beginning". Even greater explanatory difficulties might be anticipated in the event of there being an evil power, loosed in deep time before the world began, and functioning as a "fifth-column" causal agent in God's creation. Just such an understanding does appear to permeate the Bible and it is also present in all major Christian traditions since apostolic times.

As new data emerge from scientific enquiry dialogue will continue between scientists and interpreters of the Bible. This conversation, now hundreds of years old, can be expected to present new challenges to Christian understanding. The integration of programmed cell death into this discussion provides an excellent example of this process.

QUESTIONS

1. Do you see the programmed death of cells as being "death" in the same sense as that conveyed by the death of a simple organism, such as a worm? What about the death of a human being? Are there different dimensions of death, or is there perhaps a hierarchy of death, lower levels of which may have regularly taken place in Eden without violating traditional Christian understanding of pre-fall perfection and deathlessness?

2. Which of the models discussed at the end of this paper do you regard as representing the most honest compliance with firstly, the biblical data and secondly, the scientific data? Do you sense any tensions between your preferred biblical position on, for example, the origin of death, and your preferred scientific position? How should a modern Christian best resolve such difficulties?

3. Are you surprised to learn that death mechanisms are programmed into life forms at the most fundamental level, i.e. the genome? Would you expect

any programmed cell death at all in the New Earth?

4. Do you see the usefulness of the Bible as a modern guide to faith as compromised in any way by the fact that its writers obviously didn't know much of what we know about the natural world and the way life, for example, works?

5. Do you see any moral difference between the incidental death of a cell, as in necrosis, and programmed cell death? For that matter, is there any moral difference between the accidental death of a human being and an execution?

REFERENCES:

[1] "He will swallow up death for all time, And the Lord GOD will wipe tears away from all faces, And He will remove the reproach of His people from all the earth; For the LORD has spoken" (Isa 25:8, NASB)., "The last enemy that will be abolished is death" (1 Cor 15:26, NASB).

[2] "Then the LORD God said, 'Behold the man has become like one of Us, knowing good and evil; and now, he might stretch out his hand, and take also from the tree of life, and eat and live forever'– therefore the LORD God sent him out from the garden of Eden, to cultivate the ground from which he was taken. So he drove the man out; and at the east of the garden of Eden He stationed the cherubim and the flaming sword which turned every direction to guard the way to the tree of life" (Gen 3:2224, NASB).

[3] ". . . and He will wipe away every tear from their eyes; and there will no longer be *any* death; there will no longer be *any* mourning, or crying, or pain; the first things have passed away" (Rev 21:4, NASB)., ". . . On either side of the river was the tree of life, bearing twelve *kinds* of fruit, yielding its fruit every month; and the leaves of the tree were for the healing of the nations. There will no longer be any curse; and the throne of God and of the Lamb will be in it, and His bondservants will serve Him" (Rev 22:2, 3, NASB).

[4] "For God so loved the world that He gave His only begotten Son, that whoever believes in Him shall not perish, but have eternal life" (John 3:16, NASB).

[5] "And he ordered us to preach to the people, and solemnly to testify that this is the One who has been appointed by God as Judge of the living ('quick', KJV) and the dead" (Acts 10:42, NASB).

[6] "Only you shall not eat flesh with its life, *that is*, its blood" (Gen 9:4, NASB)., "For *as for the* life of all flesh, its blood is *identified* with its life. Therefore I said to the sons of Israel, 'You are not to eat the blood of any flesh, for the life of all flesh is its blood; whoever eats it shall be cut off'" (Lev 17:14, NASB)., "Only be sure not to

eat the blood, for the blood is the life, and you shall not eat the life with the flesh" (Deut 12:23, NASB).

[7] In Genesis 1:11 – 12, in which passage is depicted the creation of vegetation, there is no mention of life. However, in vs 21, in connection with the creation of birds and fish, we find the expression "every living creature that moves" (NASB). Furthermore, in Gen 9:3 we find God allowing "every moving thing that is alive" to be used as food even as He had earlier given humans the "green plant" as food. Nowhere, so far as the authors could find, does the Bible explicitly speak of the "death" of plants, although there are some confusing references, for example, Eze 31:14. These points are often presented by writers within the Creation Science movement, such as John D. Morris – see http://www.icr.org/article/1099/ (downloaded 6/6/2013).

[8] Timms, B. (2012). Seasonal study of aquatic invertebrates in five sets of latitudinally separated gnammas in southern Western Australia. *Journal Royal Society of Western Australia*, *95*, 13-28.

[9] See http://www.nobel.se/medicine/laureates/2002/presentationspeech.html for a brief summary of the basis of this prize.

[10] Extreme examples include the thermophilic bacteria that live in deep sea vents where volcanic material is released into water. Here organisms live at many atmospheres of pressure and at temperatures above 100 °C. Other examples are halophilic organisms that live in the salt pans on salt lakes and only grow at NaCl concentrations greater than 1M. Although such extremaphiles live at the extremes of environmental conditions they nonetheless have a narrow range of temperature and environmental conditions that allow their survival and growth.

[11] Kerr, J. F. R., Wyllie, A. H., and Currie, A. R. (1972). Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer*, *26*, 239-257.

[12] Yuan, J. and Kroemer, G. (2010). Alternative cell death mechanisms in development and beyond. *Genes & Development*, *24*, 2592-2602.

[13] Clark, W. R. (1996). *Sex and the Origins of Death*. New York: Oxford University Press, 31.

[14] Kanold, P. O. (2009). Subplate neurons: crucial regulators of cortical development. *Frontiers in Neuroanatomy*, *3*,1-9.

[15] Courchesne, E., Mouton, P. R., Calhoun, M. E., Semendeferi, K., Ahrens-Barbeau, C., Hallet, M. J., Barnes, C. C. and Pierce, K. (2011). Neuron number and size in prefrontal cortex of children with autism. *Journal of the American Medical Association*, *306*(18), 2001-2010.

[16] Medawar, P. (2013). Nobel Lecture: Immunological Tolerance. Nobelprize.

org. Nobel Media AB. Web.3 Oct 2013. <http://www.nobelprize.org/nobel_prizes/medicine/laureates/1960/medawaw-lecture.html>.

[17] Doubling each time, an expansion over 8-10 cycles will produce 2^8 (256) to 2^{10} (1024) new cells for each initial responder.

[18] Clark, W. R. (1996). *Sex and the Origins of Death*. New York: Oxford University Press, 93-95.

[19] Lippens, S., Denecker, G., Ovaere, P., Vandenabeele, P. and Declercq, W. (2005). Death penalty for keratinocytes: apoptosis versus cornification. *Cell Death and Differentiation*, *12*, 1497-1508. Also Lippen, S., Hoste, E., Vandenabeele, P., Agostinis, P. and Declercq, W. (2009). Cell death in the skin. *Apoptosis*, *14*, 549-569.

[20] See for details Doctor, K., Reed, J., Godzik, A., and Bourne, P. (2003). The apoptosis database. *Cell Death Differ*, *10*(6), 621-633.

[21] Levine, M. and Tjian, R. (2003). Transcription regulation and animal diversity. *Nature, 424*(6945), 147-151.

[22] Fisher, H.J. (1987). The enigma of ecology. *Record*, *92*(11), 4-5.

[23] Provonsha, J. (2000). 'Creation/Evolution Debate in Light of the Great Controversy', in Hayward, J. L. (ed.), "*Creation Reconsidered: Scientific, Biblical and Theological Perspectives*". California: Assoc. of Adventist Forums, 303-311.

[24] Gen 1:28.

[25] Gen 2:7, 8.

[26] Job 39:14,15 – God seems unconcerned about the wasteful and heedless ostrich; Job 38:39 & Ps 104:21– the young lions roar after their prey, and seek their meat from God; Job 38:41 & Ps 147:9 – God feeds the ravens; Matt 8:31, 32 – Christ sends the devils into the herd of swine which immediately drown; Luke 5:4-7 – the huge catch of fish.

[27] See Genesis 1-3; Isa 11:6-9; Isa 65:25 and Rev 22:3.

[28] White, E. G. (1908). *Steps to Christ*. Washington, DC: Review and Herald, 9.

[29] White, E. G. (1958). *Patriarchs and Prophets*. California: Pacific Press, 62. Possibly also reflecting a view of the longevity of flowers in Eden Ellen White reported an early vision in which she seemed to be in the New Earth. While plucking some flowers she cried out, "They will never fade." (White, E.G. [First published 1882] (1945). *Early Writings*. Washington, DC: Review and Herald, p18). A similar statement by the same author appears elsewhere. "This earth,... purified with fire, then ... will be much more beautiful. The grass will be living green, and will never wither. There will be roses and lilies, and all kinds of flowers there. They will never blight or fade, or lose their beauty and fragrance" (White, E.G. (1976). *Maranatha*. Washington DC: Review & Herald, p355).

[30] White, E. G, (1958). *Patriarchs and Prophets*. California: Pacific Press, 48.

[31] Rev 22:2.

[32] See Brand, L. (2003). 'What are the Limits of Death in Paradise?', paper presented at the South Pacific Division Faith and Science Conference at Avondale College, July 11-14.

[33] See for example: Ball, B. (ed), (2012). *In the Beginning*. Idaho: Pacific Press., Gibson, L. J., and Rasi, H. (eds), (2011). *Understanding Creation*. Idaho: Pacific Press., Clausen, B. and Wheeler, G. (2006). *The Book of Beginnings*. Hagerstown, MD: Review and Herald., Roth, A. (1998). *Origins: Linking Science and Scripture*. Hagerstown, MD: Review and Herald. and Brand, L. (1997). *Faith, Reason and Earth History*. Berrien Springs, MI: Andrews University Press.

[34] In his lecture, "Adventist Interpretations of Genesis 1:1,2", presented at Avondale College on May 14, 2011, Gerhard Pfandl acknowledged the presence of this viewpoint with the statement, "The third view in our Church (Adventism) is theistic evolution. As I indicated this morning for a number of years now theistic evolution has been held by several scientists and theologians". Pfandl mentioned Fritz Guy by name. Later in his lecture this point was repeated: "Now, in addition to the two views indicated in this quote we find now also a third view, theistic evolution, being promoted in the Church today." These comments reflect awareness of long-age and evolutionary concepts explored in several of the essays in Hayward, J. L. (2000). *Creation Reconsidered: Scientific, Biblical, and Theological Perspectives*. California: Association of Adventist Forums., particularly those by Taylor, E. and Ritland, R.M. Also, although not explicitly espousing theistic evolution, the book: Bull, B., Guy, F. & Taylor, E. (eds.), (2006). *Understanding Genesis: Contemporary Adventist Perspectives*. California: Adventist Today, sets up a framework which allows theistic evolutionary options.

[35] See for example: Collins, F. (2006). *The Language of God*. NY: Free Press., Colling, R. G. (2004). *Random Designer*. IL: Browning Press., Falk, D. R., (2004). *Coming to Peace with Science*. IL: Intervarsity. and Peters, T. & Martinez, H. (2003). *Evolution from Creation to New Creation: Conflict, Conversation, and Convergence*. Nashville, TN: Abington.

[36] See Taylor-Brown, E. & Hurd, H.2013). The first suicides: a legacy inherited by parasitic protozoans from prokaryote ancestors. *Parasites and Vectors*, *6*,108. Also Ratcliff, W. C., Denison, R. F., Borrello, M. and Travisano, M, (2012). Experimental evolution of multicellularity. *PNAS*, *109*, 1595-1600.

[37] Gray, M. W., Burger, G. and Lang, B. F. (1999). Mitochondrial evolution. *Science*, *283*, 1476-1481.

[38] See Koonin, E. and Aravind, L.

(2002). Origin and evolution of eukaryotic apoptosis: the bacterial connection. *Cell Death Differ*, *9*(4), 394-404., and Bridgham, J., Wilder, J., Hollocher, H., and Johnson, A. (2003). All in the family: evolutionary and functional relationships among death receptors. *Cell Death Differ*, *10*(1), 19-25.