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AN ADAPTATIONIST VIEW OF APOPTOSIS

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ABSTRACT
A cell’s decision whether to undergo apoptosis (cell suicide) is examined here from an adaptationist perspective, rather than a mechanistic one. External and internal inputs to the cell’s protein-based information processing network are used in making this decision, with the cell factoring in its replaceability. A system in which each cell takes primary responsibility for deciding its own fate has great adaptive value because it harnesses each cell’s self-knowledge rather than waiting for external cues to be recognized by other cells. Cell self-destruction can be an important selective mechanism, potentially leading to better performance of tissues over time. However, reliance on cells to monitor themselves has a flaw, since cells may incur selfish mutations that impair their apoptotic responsibility. The tight control exerted over somatic cells serves to check selfish genes involved in neoplasia and viral infections. Germ cells appear to be similarly monitored, both by other germ cells and by supporting follicular or Sertoli cells, thus maintaining the advantages offered by an apoptotic system. The adaptationist approach views the limited replacement of neurons and cardiac myocytes as likely to have net survival value. The linkage of these cells into a network with their neighbors throughout a lifetime allows for a precisely functioning team of cells expected to compensate for gradual declines in individual cell functionality. Replacement of apoptotic cells with naive cells might decrease brain functionality and might risk upsetting the conduction of cardiac impulses. The evolutionary viewpoint lends itself to new hypotheses, but only the boldest speculator would have predicted a system in which cells are given primary responsibility for deciding whether to kill themselves when they deem it beneficial to the organism.

INTRODUCTION
APOPTOSIS is the orderly process of cell death that requires the functional cellular machinery of gene expression and protein synthesis (Kerr et al. 1972; Wyllie 1987; Smith et al. 1994). Frequently referred to as programmed cell death, apoptosis is typically contrasted with necrosis. The term “oncosis” is being proposed for the process leading to cell death when the cell is not a willing participant in its own death (Majno and Joris 1995; Trump 1995). The apoptotic decision is defined here as the cell’s decision to kill itself or continue living (Steller 1995; Thompson 1995). Apoptosis is thought to be as important a function...
as cell replication, and the mechanics of apoptosis have been the subject of intense scrutiny.

Apoptosis occurs in settings where cells are no longer needed, such as during tissue development, in healing tissues, among oocytes and their follicular cells, and in tissues undergoing atrophy because of reduced functional requirements. Apoptosis is also prominent in cases where cells may be directly harmful, such as lymphocytes targeted at self antigens, residual neutrophils at resolving inflammatory sites, virally infected cells, and damaged cells that might become neoplastic. Because apoptosis does not involve leakage of cell contents before the dying cell is phagocytized by neighboring cells or macrophages, the process is a "clean" way of disposing of a cell, one that does not lead to inflammation or spillage of virions (Clouston and Kerr 1985). Apoptosis also occurs in situations where cells are exposed to potentially lethal insults of any kind (Raff et al. 1993; Thompson 1995). Severely damaged cells are directly killed via oncosis or necrosis, while less damaged cells may undergo apoptosis. In this situation, apoptosis would tend to prevent neoplasia by removing mutated cells, and would allow the tissue to be repopulated with the progeny of less damaged (or more resistant) cells.

The purpose of this review is to consider (1) a cell's apoptotic decision, (2) apoptosis as a system, and (3) the lack of replaceability of lost cells in certain tissues, using an adaptationist (evolutionary) approach rather than a mechanistic one. The adaptationist approach hypothesizes how a system could or should function, and fills in the details later. The mechanistic approach, on the other hand, builds upon the discovery of details that explain how a system actually functions, and only later hypothesizes about the possible adaptive value of those details. Implicit in the adaptationist approach is the consideration of alternatives to existing systems; utility of this perspective has been particularly well described by Nesse and Williams (1994) and Dennett (1995). It is often not sufficient to ask why a feature exists in its present form; understanding it may require seeking other perspectives. The perspective employed here, in combination with the adaptationist approach, builds on the view that cells have robust information processing mechanisms not unlike those of a complex multicellular nervous system.

The apoptotic decision will be considered in this review to be a true decision on the part of each cell, based upon inputs to the cell's information processing network. This concept—that information is considered by the cell in making its decision—is derived from several sources: (1) Koshland (1977) noted that the processes driving behavior of individual cells are analogous to those of animals and humans (e.g., judgment, memory, choice, and discrimination), (2) Braitenberg (1984) described how imaginary artificial beings with increasingly complex behavior and psychological attributes could be synthesized through a series of rather simple steps involving information processing networks, and (3) Bray (1990, 1995) noted the similarity of protein-based cellular information processing to neural networks.

This psychological view of cell information gathering, information processing, and response requires an awareness of the abundance of inputs available to cells. Beyond the specific ligands recognized through cell surface receptors and signal transduction proteins, any perturbation of a cell (chemical or physical) can potentially be detected. Dennett (1971) noted that the best way to predict the next move of a chess-playing computer is to assume that the computer intends to win, rather than by analysing its circuitry; similarly, consideration of a cell's intentionality also offers a useful approach in an adaptationist analysis. Although terminology is used that some may consider anthropomorphic, the intent is to compare the information processing of cells with those of animals (at whatever level of neural development the reader feels is appropriate), since the fundamental processes are similar. I will consider those areas of apoptosis (and cell replacement) where the combination of an adaptationist approach with the cellular information processing perspective leads to potentially useful insights. Some of the points discussed are not original, and others are of a speculative nature, derived from this analysis.
CELLS HAVE A SINGLE COMMON GOAL

The reliance on apoptosis as a mechanism for removing unneeded or dangerous cells depends on the absence of genetic conflict among cells, since each cell’s goal is to transmit its genetic information through time (Dawkins 1995). Under normal situations the cells in an organism are virtually genetically identical, although conflicts involving selfish genes can arise in neoplasia, in viral infections, and among haploid gametes (Haig and Grafen 1991; Parker and Begon 1993). Although this review centers on multicellular animals, much of the discussion may be relevant to apoptosis in plants (Greenberg et al. 1994; Levine et al. 1994; Wang et al. 1996). With the recent descriptions of programmed cell death in unicellular organisms, the evolutionary origins of apoptosis are pushed further back in time, and the degree of genetic relatedness of altruistic independent organisms thus becomes critical (Ameisen 1996).

In the following “team player analogy,” an organism is compared to a team, and each cell is a player on that team, but there is no coach; the players work toward the success of the team, regardless of whether they actually play. On such a team, we might ask: How could a team player reach a decision to step out of the game in order to improve the team’s success? The player would certainly consider the following types of information: (1) external signals concerning his performance (e.g., hearing or seeing reactions from teammates, or relative involvement in key plays), (2) knowledge of his internal state or health that is not directly apparent to others (e.g., not getting enough sleep—a temporary effect, or realizing that his headaches keep getting worse—a progressive effect), and (3) knowledge of his replaceability (e.g., having highly specialized skills not readily replaceable, or having worked with other teammates so long and closely that they have learned to compensate for one another’s weaknesses). These inputs would be used to make a comparison between the player and his teammates or his replacement, a replacement that might temporarily reduce the team’s performance. The player’s decision whether to play or quit would depend on the relative importance of each type of input. The strength and persistence of each type of input would change constantly.

INPUTS TO THE APOPTOTIC DECISION

External Inputs

Raff (1992) has suggested that the default condition for a cell is apoptosis; only the continued presence of survival factors from other cells (its social environment) keeps the cell from undergoing apoptosis. He described simple feedback mechanisms that might regulate apoptosis, such as cells being forced to compete with neighboring cells for limited amounts of survival factors. While not denying the elegance of such a simple mechanism as the competition for survival factors, in the context of this discussion, the concentration of survival factors can be viewed as information (rather important information) to be used for cell decision making. The concept of a cell constantly deciding whether to undergo apoptosis seems reasonable to the extent that the team player is always deciding whether the team would be better off without him. Thus, the apoptotic decision defined here would be answered “no” continuously and “yes” only once. The emphasis on the cell’s social situation is appropriate, since intercellular communication, which informs a cell about its performance in relation to its neighbors, is critical for making the apoptotic decision. This intercellular communication can occur through extracellular chemical messages, gap junctions, or mechanical signals via the “extended cytoskeleton” that physically links cells directly or indirectly by way of the extracellular matrix (Ingber et al. 1994). Knowledge of whether neighboring cells had decided to undergo apoptosis or replication would be especially valuable information. A cell recognizing that its neighbor had decided upon apoptosis would suddenly find itself relatively more important. The asynchrony of apoptosis seen in vivo or in vitro studies, despite seemingly identical cell populations that receive the same treatments, most likely reflects the subtle “psychological” differences among cells; these differences are magnified by the effect that apoptosis of neighboring cells has upon its own apoptotic decision. This difference in decision making, which appears stochastic because we are not privy to the cell’s inputs and
their relative weights, is at the heart of the question of differing behaviors by seemingly identical cells.

**Internal Inputs**

Internal as well as external inputs are clearly crucial in making the apoptotic decision (Isaacs 1993; Steller 1995; Thompson 1995). As noted in the team player analogy, a comparison with other cells requires knowledge of one's own internal state, which includes the cell's performance level and health status. The tremendous amount of potential information available to a cell about itself (e.g., the status of its DNA, membranes, cytoskeleton, organelles, temperature, ionic concentrations) can be monitored directly or indirectly through the effects of perturbations on other components of the cell's information processing network. Presumably, a damaged cell would assess certain factors, such as injury and rate of repair, when making its apoptotic decision. A cell knows its own internal state best, just like that of our team player. Similarly, its knowledge of another cell's internal state is limited to that cell's external manifestations.

A cell's knowledge of its replaceability and the apoptotic decision

A cell's knowledge about its role or function (e.g., cell type, state of differentiation, and replaceability) within an organism is likely to be hardwired (instinctive). The knowledge of its replaceability is expected to be an important factor in its decision to undergo apoptosis. At one extreme is virtually complete replaceability of cells with a high normal turnover (e.g., epidermal and intestinal epithelium, red blood cells, polymorphonuclear leukocytes) and their stem cells; other cells with particularly high apoptotic rates include embryonic neurons and ovarian germ cells. At the other extreme are cells with little replaceability, most notably neurons and cardiac myocytes, and these cells would be expected to weigh the apoptotic decision particularly carefully.

**EMBRYONIC NEURONAL APOPTOSIS**

Embryonic brain development is characterized by a marked overproduction of neurons and prominent apoptosis of excess cells. The removal of poorly functioning or incorrectly connected neurons by apoptosis has been noted as the benefit of excess neuron formation during development (Raff et al. 1993; Ameisen 1994). Brown et al. (1994) used a computer neural network model to expand on the value of neuronal overproduction and the role of apoptosis in brain development. They found that neuronal overproduction, with subsequent deletion of neurons (even randomly), allowed substantially greater learning (problem solving ability) than that accomplished by starting out with only the necessary number of neurons. They deleted one neuron (artificial neuron) at a time from the network, and the network quickly relearned the solution. By sequential deletion and relearning, a network starting with 12 intermediate layer (or hidden) neurons that gradually dropped down to 3 neurons was considerably more likely to reach a correct solution to the problem than a network that started with 3 neurons and kept them. They noted that, while random removal of neurons with subsequent retraining was three times more effective in their model than starting with just 3 neurons, selecting out neurons based on their contribution to learning the solution was five times more effective than starting with 3 neurons. Brown et al. (1994) addressed the question of how a nerve/neuron can know how much contribution it is making relative to other neurons/neurons by its performance. They developed an algorithm whereby a neuron that had relatively little change in its output regardless of input was presumed to be contributing little to solving the problem. Thus, by using changes in firing pattern as a criterion, the neurons were able to determine their relative value. As fewer neurons remained in the network, each contributed increasingly to the solution, thus automatically halting further neuron deletion. This computer model thus placed neuronal overproduction in a new light, in addition to showing the utility of apoptosis as a selective tool.

**APOPTOSIS IN OVARIAN GERM CELLS**

Apoptosis is an especially prominent feature of mammalian ovarian germ cells (Coucouvanis et al. 1993). Baker (1963) calculated that in the embryonic human ovary there are roughly 6.8 million germ cells, peaking at the
fifth month postconception. By birth there are only about 2 million germ cells, with further declines owing to apoptosis before and after puberty. Of the 6 to 7 million germ cells, 400 is the maximum number likely to be ovulated. Thus we see that a vast excess of germ cells is formed, and that the excess cells commit suicide. It would be astounding if these cells simply undergo strictly random apoptosis, since there would have been no apparent reason for such a large number to be formed. Given that cells can have some knowledge of their internal state and can use that information to make the apoptotic decision, then these otherwise genetically identical cells must be selecting among themselves which germ cells should survive. The precise criteria they are using to make the apoptotic decision remains to be determined, but one might speculate that various tests of function are conducted (Cohen 1975; Coucounanis et al. 1993).

Another intriguing feature of early ovarian germ cells is that daughter cells are linked by cytoplasmic bridges large enough to allow passage of organelles (Dym and Fawcett 1971; Zamboni 1972). Thus the oogonia (mitotically active germ cells) and early oocytes (mitotically inactive germ cells) are interconnected throughout the ovary in such a way that lineage can theoretically be determined. At present, the function of these cytoplasmic bridges has not been established, but an adaptive function is presumed, since the complete division seen in other cells would otherwise be expected. The cytoplasmic bridges close off as the oocytes become surrounded by developing follicular cells, which then establish numerous gap junctions with each oocyte. The linkage of the germ cells through lineage could serve as a way to pass information on an apoptotic decision (or an inclination toward apoptosis) back to ancestral cells and forward to descendant cells. This information might convey a message that the lineage has a defect and apoptosis should be considered more strongly. It is noteworthy that groups of oogonia and early oocytes have been observed to degenerate together (Weir and Rowlands 1977). Not only would this additional input help a germ cell to flag potential defects that it might not have found, but more importantly this could serve as a means of controlling rogue germ cells deficient in their apoptotic propensity and responsibility. If germ cells, with an irresponsible disinclination to undergo apoptosis, were to be passed on to future generations, then the advantages of apoptosis (in both somatic and germ cells) would be lost. Thus it is no coincidence that germ cells capable of passing on an apoptotic defect are “escorted.” Germ cells are first tightly linked to their mother and daughter cells via intercellular bridges, and later are dependent on the supporting follicular cells, which have the capability of ending the oocyte’s life (by undergoing apoptosis themselves).

**Apoptosis and Control of Testicular Germ Cells**

Selection of male germ cells is less dependent on apoptosis; instead it relies more predominantly on competition among sperm in fertilizing the ovum. While a female benefits by ensuring that only the very best ova are ovulated (especially if the cost of resources per offspring is high), a male individual is required to have large numbers of sperm in order to ensure fertilization. This is owing in part to the female reproductive tract’s demands for large numbers of sperm (Cohen and McNaughton 1974; Roldan et al. 1992). A possibly related reason for large numbers of sperm is to overcome sperm competition from other males (Parker et al. 1972; Parker and Begon 1993; Manning and Chamberlain 1994). Nevertheless, it may be in the interest of an individual male that a genetically defective sperm does not fertilize an ovum. Thus it is notable that there is substantial germ cell apoptosis within the testis (Roosen-Rung and Leik 1968; Dym and Fawcett 1971). As with germ cells in the ovary, those in the testis are also linked with their ancestors and descendants by cytoplasmic bridges. Again, there is no currently accepted explanation for an adaptive advantage for this communication among germ cells. For spermatogonia and spermatocytes, which are genetically identical except for recent mutations, the explanation given above for ovarian germ cells (information transfer relating to the apoptotic decision) may be adequate. However, the finding of Braun et al. (1989) that the linkage via cytoplasmic bridges of the genetically different haploid sper-
matids makes them functionally diploid, suggests an even more important function for the cytoplasmic bridges between spermatids.

Because the haploid spermatids and sperm typically share one-half of their genes, there is an opportunity for the establishment of selfish killer or resource extractor genes that favor the survival of sperm carrying the genes for the trait, much to the detriment of sperm that do not carry those genes (Parker and Begon 1993). This threat is especially great immediately after meiosis, since each spermatid is only one-third genetically related to each of its three sibs derived from a spermatocyte (the two sets of genes are shared by the four spermatids derived from a spermatocyte, so a spermatid’s three sibs share its corresponding set of genes and two copies of the other set of genes). The cytoplasmic bridges would be expected to play an important role in discouraging potential strife among genetically different gametes, since by harming one’s sib, the spermatid would be harming itself (Haig and Bergstrom 1995). This phenomenon of selfish genes in gametes, termed meiotic drive, has been particularly well described for Drosophila and in the t locus of mice (Crow 1991; Haig and Grafen 1991; Lytle 1991; Hurst 1992). The inhibition of meiosis in female germ cells until ovulation and fertilization effectively precludes the potential for genetic conflict in the ovary among the nonidentical haploid germ cells that can occur in the testis. As with the follicular cells of the ovary, the Sertoli cells in the testis provide not only nourishment but also can provide “apoptotic input” to those germ cells deficient in this regard.

APOTOPSIS IN TISSUES WITH MODERATE CELL TURNOVER

Most cells have variable life spans and may undergo apoptosis when they are no longer needed, substantially damaged, or directly harmful. Prostatic epithelial cells are an example of cells with an intermediate life span, and have been well studied from an apoptotic point of view (Furuuya et al. 1994; Isaacs 1993). Normally about 2% of rat prostatic epithelial cells undergo apoptosis per day, and it is suggested that the membrane damage from secretion plus exposure of the cells to proteases takes its toll. Prostatic epithelium is also exquisitely hormonally responsive; upon removal of androgen (as with castration), about 80% of the prostatic epithelial cells undergo apoptosis within 7 to 10 days.

The timing of apoptosis in one cell relative to another cell, and why some cells decide not to undergo apoptosis, is of particular interest in the context of this review. A mechanistic approach would suggest that the cells are competing for scarce survival factors. Yet the informational/psychological view presented here suggests that survival factors provide information to the cells about their current value in relation to other cells. The abrupt removal of androgen by castration would affect a prostatic epithelial cell’s assessment of its usefulness to the organism as a whole. A large number of internal and external factors could influence a cell’s apoptotic decision; the information provided by low androgen levels would be expected to influence the timing and overall apoptotic decision. We might expect the balance between apoptosis and cellular atrophy, in organs undergoing seasonal or disuse atrophy, to be tipped relatively more toward apoptosis in flying animals, where weight is a critical impediment, than in land or water-based animals. Presumably any such apoptotic propensity would be programmed as an instinct into the cell’s information processing network.

APOTOPSIS AS A SELECTIVE PROCESS FOR IMPROVING TISSUE PERFORMANCE

Unequal rates of apoptosis owing to variations in cell functioning is a selective process. Well-functioning cells or particularly useful cells would be less apt to decide upon apoptosis; thus they would survive longer and presumably be progenitors of replacement cells. One can conjecture that a mechanism could exist whereby progenitor or stem cells could receive feedback on the performance of their progeny, and that this information could be used to further enhance tissue performance through differential rates of apoptosis and proliferation at the stem cell level. In tissues such as epidermis and intestinal epithelium, the lineage would be expected to be traceable via a variety of cell communication mechanisms (although not as readily as in germ cells with their large cytoplasmic bridges, as de-
scribed previously). Because of the selective power of apoptosis, we might expect that the functionality of cells in a tissue could improve with time. In this selection for improved performance, we have a genetic algorithm (repeatedly testing, selecting, and regenerating), described by Bray (1995) as the basis for the information processing network within cells to improve from cell generation to generation. Countering any selective improvement in function are age-related functional deteriorations, such as accumulating mutations, free radical-induced damage (including mitochondrial DNA mutations), and advanced glycosylation endproducts (Lee and Cerami 1992; Wallace 1994). Indeed, an important role for apoptosis as an antiaging mechanism by maintaining tissue functioning has been postulated (Tomei et al. 1994).

The well-described antiaging and antineoplastic benefits of dietary restriction appear to be attributable to the relative enhancement of apoptosis (Muskhelishvili et al. 1995). Grasl-Kraupp et al. (1994) studied preneoplastic foci in rat livers, which have enhanced rates of proliferation and apoptosis. They noted that dietary restriction both reduced proliferation and preferentially increased apoptosis in the preneoplastic cells, compared with normal hepatocytes. Additionally, they found that the livers of rats with dietary restriction had reduced numbers of preneoplastic foci and tumors compared to control rats. Similarly, James and Muskhelishvili (1994) found that dietary restriction in mice increased the apoptotic rate in the liver (and reduced the proliferative rate), which was associated with a decreased incidence of liver tumors over a three-year period. Thus there is clear experimental evidence for the selective role of apoptosis in improving tissue functionality and inhibiting aging.

Improved tissue functioning over time is notable in two tissues that use markedly different mechanisms: (1) individual cell learning (making adaptive changes as a result of experience or instruction)—a specialty of neurons, and (2) differential cell selection through apoptosis coupled with proliferation—a specialty of lymphocytes. The nervous system’s functionality improves with time through the ability of individual neurons to learn (the learning of the overall task being dependent upon the learning of each neuron involved). At the other extreme, the improved performance of the immune system owing to selective apoptosis of relatively unnecessary lymphocytes and proliferation of important ones is a clear example of improved functioning with time. One would expect that in other cell types, learning by individual cells, along with apoptosis of cells relatively poor at learning, would be a powerful combination, but at present this possibility remains speculative.

It is clearly important that the immune system in an individual be able to evolve to compete in the arms race with rapidly evolving potentially pathogenic microorganisms (Levin and Bull 1994). As mentioned, the apoptosis of underutilized lymphocytes makes this selective process possible. Nevertheless, one could see where apoptotic selection, combined with individual cell learning (including selection for cell learning), could have considerable utility in host defense, if it were to occur. For instance, one function of Kupffer cells (the fixed macrophages in the liver derived from the bone marrow) is to protect the systemic circulation from bacterial invasion from the intestine. Kupffer cells are well endowed with receptors that recognize bacteria, in part owing to receptors for lipopolysaccharide (LPS) in the outer cell wall of gram negative bacteria. Free LPS shed from dead or dividing bacteria, however, is not in itself a threat—it may simply be noise that should be ignored, or at other times it may indicate some degree of bacterial threat. Thus a Kupffer cell that could quickly learn effective strategies for interpreting potential bacterial signals and respond effectively (killing bacteria, while minimizing false alarms and damage to adjacent cells), would be especially valuable. [The prominent role of Kupffer cells in causing hepatic damage has been reviewed by Laskin (1994).] Selection through apoptosis of less adroit Kupffer cells could effectively raise the rate of learning. The diminished responsiveness (tolerance) that occurs following repeated experimental doses of LPS or tumor necrosis factor suggests individual cell learning by macrophages. Clearly, cells have the capability for both learning and self-destruction, and the rapid evolutionary capability of surrounding microorganisms
during an individual's lifetime would be a strong selective force. At present, the enhanced performance over time of defensive cells other than lymphocytes (e.g., epithelial cells, endothelial cells, and macrophages) is speculative.

TISSUES LACKING REGENERATIVE CAPABILITY

Two tissues notorious for lacking significant regenerative ability are neurons in the adult brain and myocytes in the heart; at present there is no accepted explanation for why this should be so for either organ (Compston 1994; Gulati 1995). The mechanistic response is that these tissues consist of postmitotic cells, although there appears to be slight proliferative capacity for cardiac myocytes (Liu Y et al. 1995). The neurotrophic theory postulates that limitations on growth factors and neuronal responsiveness to them inhibit neuronal replication (Raff et al. 1993). These mechanistic explanations, however, still do not answer the question of why that should be. Given that most cell types have regenerative capability, and that cell capabilities continue to offer surprises, it is reasonable to assume that this lack of regenerative capacity has benefits that outweigh the disadvantages. Indeed, Tomei et al. (1994) appear to be on track with their comment that “[i]n many cases, these cells have such intricate architectural features and contact points that their replication is of necessity constrained or totally precluded” (p.385). The combination of views presented here—that organisms have cells linked in networks and that cells can be viewed as fiercely loyal or altruistic team members—suggests a speculative answer along the lines suggested by Tomei et al. (1994).

Absence of Replacement Neurons

Since neurons do not proliferate substantially in postnatal life, these cells have spent a lifetime together as part of a network; the neurons developed together and grow old together. The results of this teamwork are clearly evident in the brain. Memories are made by the cooperative efforts of these neurons that have honed long-term relationships with specific cells, even with cells in distant parts of the brain. A key feature of network learning using parallel distributed processing is that it is robust. As seen with the computer model of neuronal apoptosis by Brown et al. (1994), neurons in a network can compensate for the gradual loss of other neurons. Within the brain, neurons gradually lose functionality as the insults of a lifetime accumulate. However, the cells in the network appear to compensate for this gradual change in inputs from aging neurons, since the overall output is little changed. Apoptosis of neurons may even occur, although the criteria for deciding upon apoptosis clearly differ from those of readily replaceable cells. Should a defective or dead cell be replaced? The team player analogy is apt. Over a number of years, players on a team that demands high skill levels and close teamwork would be able to recognize and adapt to the special strengths and weaknesses of each player. This adaptation would occur even as a player’s ability weakens, eventually forcing him to quit. It is easily seen that an untrained replacement would not fit in with a team that has taken months or years to master the required skills and cooperation needed to succeed; a team would perform better without the new player. During the long period of training, the replacement would constantly be forcing the rest of the team to make radical adaptations. Isacson et al. (1995) reported that when pig neurons were transplanted into rat brains, the transplanted neurons were still making new connections for at least six months. The hypothesis presented here—that replacement of highly specialized cells by untrained, inexperienced cells would be more disruptive than beneficial to neural network functioning lends itself to computer modeling.

Absence of Replacement Heart Muscle Cells

As with neurons, the myocardial cells have been associated with their neighbors for a lifetime, adapting to cell-to-cell variations in conduction ability and contraction strength. Unlike neuronal function, myocardial cell functions (transmitting electrical impulses and contracting) appear to be rather straightforward. One would expect that a replacement cardiac myocyte should be able to become functional rather quickly. But because every heartbeat is critical (since arrhythmias can be fatal within minutes), there is little leeway for experimentation or training. Perhaps
in the short period of time when a newly created replacement cell is establishing contacts (gap junctions) with its new neighbors, there might be enough disruption of electrical impulse conduction to start an arrhythmia. Certainly, the chances of a single replacement cell setting off a fatal arrhythmia would be miniscule, but the cumulative chances of a disruptive effect of multiple simultaneous replacement cells entering the myocardial network might tip the balance such that it is safer to not replace deteriorating or dead myocardial cells. Again, this speculation lends itself to computer modeling.

THE RESPONSIBILITY OF APOPTOSIS

Given that a cell knows more about itself than does any other cell, we see the great benefit of the system of apoptosis. Rather than entrust the death decision solely to “enforcer” cells, the organism benefits from the more accurate assessment of cell status obtainable only by allowing each cell to take primary responsibility to decide when, or if, it should die. Given this huge responsibility, it is obvious why there are so many pathways to apoptosis and why they should be looked upon as safeguards rather than redundancies.

APOPTOSIS AND NEOPLASIA

The importance of apoptosis in preventing neoplasia is well described. In the simplest terms, when more cells proliferate than die, a tumor will result (Kerr et al. 1972; Isaacs 1993; Barrett and Preston 1994; Thompson 1995). In recent years, tumor suppressor genes and their protein products, many of which are involved in the induction of apoptosis, have been given equal status in their ability to prevent neoplasia as have the oncogenes (inducing cell proliferation) in their ability to cause neoplasia. The realization that an oncogene, c-myc, can also induce apoptosis points out the importance to the organism of keeping cell proliferation under tight control (by enhancing the cell’s sensitivity to apoptosis) (Evan et al. 1992). The majority of human neoplasms examined have been found to have a mutation affecting at least one of the genes involved in apoptosis, with over half having a defective p53 gene (Ashwell et al. 1994). Indeed, control of potentially neoplastic cells has been suggested as the primary evolutionary function of apoptosis (Umansky 1982).

Where does apoptosis fit in with the other methods an organism has of preventing neoplasia? Since under most circumstances neoplasia is dependent upon successive mutations, the first defense against neoplasia is to monitor the DNA and repair any damage. The second line of defense would be for the cell to monitor its own behavior and health (checking on its ability to repair DNA damage), and to undergo apoptosis if: (1) it recognizes that its own behaviors (or even inclinations) are deviant, or (2) it appears that there may be significant irreparable DNA damage.

It is noteworthy that free radicals are potent inducers of apoptosis (Buttke and Sandstrom 1994). This is an adaptive linkage, since a cell does not have to assess the health of each of its functions, but could simply note that a certain level of free radical exposure had occurred, and assume that a corresponding level of damage had occurred. Evidence that free radicals are used as signals by cells in making the apoptotic decision has been recently reviewed (Khan and Wilson 1995).

The third line of defense is input from, or action by, other cells. This line of defense is employed for cells with abnormal or inappropriate behavior that will not undergo apoptosis on their own (based on inputs that would normally be expected to induce apoptosis). Here the “encouragement” of neighboring cells may be manifest through messages passed via gap junctions, considering that cell communication via gap junctions tends to be reduced when cells get proliferative signals from tumor promoters (Hotz-Wagenblatt and Shalloway 1993; Goldberg and Bertram 1994; Trosko and Goodman 1994). Failing this and other encouragement from neighboring cells to induce the “apoptotically impaired” cell to undergo apoptosis, cytotoxic lymphocytes may be called upon to offer more professional “assistance.” Interestingly, even these professional killer cells preferentially induce apoptosis over direct oncotic lysis (Raff et al. 1993; Berke 1995; Steller 1995). However, it has been noted that while the killed cells have the morphologic features of apoptosis, the death need not be voluntary (Traparni and Smyth 1993; Ameisen 1994). Thus the organism is protected from selfish DNA by cells first re-
pairing themselves, then killing themselves, or finally being killed (Nesse and Williams 1994). In theoretical terms a perfectly functioning apoptotic system would prevent all neoplasia, since it would have a cell kill itself before the cell ever started proliferating out of control (just as a perfectly functioning DNA repair system could prevent all nonepigenetic neoplasia, and likewise a perfectly functioning surveillance system could prevent all neoplasia).

**APOTOPSIS AND VIRUSES**

Similar mechanisms apply to viral infections, which also involve selfish genes. Virally infected cells can recognize their altered internal state and attempt to undergo apoptosis, but may be thwarted by antiapoptotic viral proteins (Clem and Miller 1994; Vaux et al. 1994; White and Gooding 1994). Apoptotic induction by cytoxic T-lymphocytes is then needed to control the infection. One can envision a continuum of control of a virally infected cell’s information processing network, from where the cell is in charge (and the virus is an annoyance), to where control is contested, to where the virus has usurped the cell’s decision-making network. Correspondingly, the cell would be able to contribute less and less to its demise. Thus it is not surprising that cytoxic lymphocytes have a variety of methods for inducing death in target cells (Liu C-C et al. 1995; Smyth and Trapani 1995).

**THE FLAW OF APOPTOSIS AS A SYSTEM OF CONTROL**

A major adaptive benefit of apoptosis as a system of control is that it harnesses each cell’s self-knowledge rather than waiting for external cues to be recognized by other cells; the flaw of cells having the primary responsibility for recognizing their own relative value is that a cell can incur damage that impairs its apoptotic responsibility. A cell with a compromised apoptotic mechanism will gain a survival advantage over the normal and responsible altruistic cells. Raff (1992) pointed out this price of apoptosis in the context of cells competing for limited survival factors: cells that compete best or require the fewest survival factors will be selected, with neoplasia the possible consequence. Viewed in another context, a mutated gene impairing apoptosis might be considered to be a selfish gene, because it makes the cell less of a team player through its own enhanced survival. Of course, in somatic cells this selfish gene would be limited to the life of the organism. Germ cells are closely linked to other germ cells and to specialized escort cells, which have the power to ensure that the benefits of apoptosis are not lost to future generations. The flaw in apoptosis as a system of self-control might be termed the “kamikaze conundrum”—the problem of selecting for cells so loyal that they would willingly die for the cause, but in passing this destructive testing, they are no longer present to replicate.

**CONCLUSION**

The primary benefits of apoptosis are the removal of cells that are no longer needed or that are dangerous, and containment of potentially harmful cell contents. These functions could have been performed by professional surveillance/scavenger cells or by neighboring cells. Instead, the responsibility for these functions rests with the individual cell, which makes the apoptotic decision based on a myriad of inputs into its information processing network. The major adaptive advantage of individual cell responsibility is that each cell is privy to considerably more information about itself than are other cells. The cell’s knowledge of its own relative importance at any instant is heavily dependent on intercellular communication. The flaw in reliance on this cell altruism is that relatively irresponsible cells tend to flourish. Thus there are mechanisms whereby other cells can help control both apoptotically irresponsible somatic cells (to prevent neoplasia) and germ cells (to prevent loss of the advantages of apoptosis in the offspring). The extent that apoptotic selection acts as a genetic algorithm enhancing tissue performance (and acting to counter the effects of aging) remains to be determined. While I have used an adaptationist viewpoint to generate these hypotheses, none of them even begin to approach the boldness needed to have predicted that cells are given the primary responsibility for the decision to kill themselves when necessary.

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