LAUDATIO HONORING PROF. JOHN F.R. KERR AND PROF. H. ROBERT HORVITZ RECIPIENTS OF THE PAUL EHRLICH AND LUDWIG DARMSTAEDTER PRIZE AWARDED ON MARCH 14, 2000

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Life and death are such fundamental questions of human beings that they have been a privilege of philosophy and religion from the primitive human societies to the recent evolved cultures. The Paul Ehrlich and Ludwig Darmstaedter Prize for the year 2000 is awarded to two scientists who, by their initial discovery and seminal work in the field of apoptosis, were able to provide a rational, scientific answer to such fundamental questions. I submit this discovery well meets the high expectations of the first Paul Ehrlich and Ludwig Darmstaedter Prize of the new millennium.

Apoptosis is perhaps the most revolutionary concept ever introduced in biological sciences, because it shows that death is a fundamental part of life and that active and well programmed death is necessary for life to progress. How did the recipients of today's prize arrive to the discovery that life and death are part of the same process and that one cannot exist without the other?

Naturally occurring cell death had been described many times already during the nineteenth century, mainly by German scientists. The first report that cells die naturally in development was by Carl Vogt in 1842, who described cell death in the notochord and adjacent cartilage of metamorphic toads. The next landmark was August Weismann who in 1864 described massive cell death in pupating diphthera. In 1872 Stieda described chondrocyte death during endochondral ossification. In 1885 Flemming described the natural regression of ovarian follicles and he called it "chromatolysis", a word that was used to describe this type of cell death for the following thirty years. However, in all these cases the cell death observed was not considered an important phenomenon, rather as an involution or a degeneration, of living tissues. The study of naturally occurring cell death lost interest at the beginning of the twentieth century and it was taken up again only in the second half of this century. The first reports again described natural cell death as an involution of phylogenetic vestiges and tissue degeneration.

The vision of naturally occurring cell death changed completely in 1972 when J. F. R. Kerr (the recipient of the today's prize) together with his collaborators A. H. Wyltie and A. R. Currie described in a paper in the *British Journal of Cancer*, that natural cell death is not an involution or a degeneration of tissues, but an active, inherently programmed phenomenon essential for organ development. The difference in the vision of the phenomenon was dramatic: natural cell death, that up to that point had been considered negative, degenerative, destructive, suddenly became part of a positive, programmed, constructive process which is necessary for development. Prof. Kerr, fully aware of the implications of his discovery, decided that a new name was needed for this type of natural cell death and called it "apoptosis". In the same paper, Prof. Kerr described with a remarkable precision the morphological features of the apoptotic cells.

The new vision of cell death, now seen as an active, programmed morphological event involved in cell turnover in healthy adult tissues and responsible for focal cell elimination during development, took almost a decade to enter into the molecular world. This happened when H.R. Horvitz (the joint recipient of today's prize), while studying the nematode *Caenorhabditis elegans*, identified genes dedicated to apoptosis and showed that cell death is the outcome of a programmed intracellular cascade of genetically determined steps. The two genes named *ced*3 and *ced*4 (where *ced* stands for cell death) were shown to be essential for the death of the 131

cells, that usually happens during the normal development of the 1000-cells worm. The above two observations provided the rationale for the ascent of apoptosis, that happened when similar genes with a similar function were discovered in humans: the protein encoded by the *ced*3 gene was found to be similar to the human protein ICE (interleukin-1 converting enzyme), a protease with a cysteine in the active site that cleaves target proteins at specific aspartic acids, and that today belongs to a large family of proteases known as caspases.

Today there is no aspect of life that does not require apoptotic death for normal functioning. Apoptosis is necessary during animal and organ development to sculpt parts of the body, or to eliminate structures that are no longer needed, such as the tail of the tadpole when this turns into a frog. Immunity relies mostly on apoptosis to get rid of self-reacting lymphocytes, to induce suicide in virus-infected cells, and to eliminate normal activated lymphocytes after they have done their job and terminate an immune response. Damaged cells are often eliminated by apoptosis: cells can somehow recognize when one of its part is damaged and commit suicide. For instance, when mitochondria are damaged they release cytochrome c, a protein that normally functions in the electron-transport process to generate ATP. Once in the cytoplasm, the protein activates the caspase-proteases inducing apoptosis. Tumor development requires apoptosis escape. This usually happens by inactivating the cancer suppressing protein p53 that induces apoptosis in abnormally dividing cells. Plant resistance genes control local cell death and limit the spread of pathogen infection. Human bacterial pathogens induce apoptosis by secreting proteins (ipaB), that specifically bind caspases and induce massive tissue apoptosis. Viruses have evolved apoptosis-blocking factors that allow survival of the infected cells.

In summary, apoptosis is strictly linked to normal development and to most of the physiological aspects of life both in animals and plants. Hence any unbalance in this process may lead to diseases such as tumors, degenerative diseases, and infections. The precise molecular knowledge of the fundamental events involved in apoptosis are today subject of intensive studies aiming at the development of drugs that may prevent or induce apoptosis to treat many diseases. A first demonstration that preventing apoptosis may cure an infectious disease by preventing neuronal death in meningitis has been reported. This is the first of many social applications that will derive from the discovery of apoptosis.

Finally, I would like to mention a few numbers that provide an idea of the impact that the concept of apoptosis is having in today's medical science and of the importance of today's prize winners in the development of this new field. From 1972 when it was first described, to March 1st 2000, 31,755 scientific papers have been published on apoptosis. It is interesting to note that in 1980, eight years after the first publication by Prof. Kerr, only six papers were published about apoptosis. Ten years later, following the seminal work of Prof. Horvitz, the paper on apoptosis had become 100. In 1999, 8045 scientific papers were published. This makes apoptosis the most popular scientific argument of medical sciences in 1999, even more quoted of the very popular HIV that in 1999 could count only 7701 scientific papers. This trend is going to continue because the understanding of apoptosis not only will increase our knowledge of living organisms, but it will be an essential part to develop new therapies.