

## TOXICOLOGICAL HIGHLIGHTS

# Apoptosis, Necrosis, or Oncosis: What Is Your Diagnosis? A Report from the Cell Death Nomenclature Committee of the Society of Toxicologic Pathologists<sup>1</sup>

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### BACKGROUND

The Cell Death Nomenclature Committee (members: Thomas Bucci, Samuel Cohen, Andrew Fix, Jerry Hardisty, Stuart Levin, Edward LeGrand, Robert Maronpot, and Benjamin Trump) held its first meeting on March 12, 1997, in Cincinnati in conjunction with the annual SOT meeting and its second meeting on June 25, 1997, at the STP's annual meeting in Beaver Creek, Colorado. The outcome of these meetings was presented to the STP membership at Beaver Creek and is summarized here. The committee intends to publish its proposals (along with criteria, rationale and examples) in *Toxicologic Pathology* and then as synopses or letters to the editor in other journals in the fields of pathology, toxicology, and cell biology.

Since the late 1980's the concept of apoptosis, as a counterpart to necrosis, has been widely accepted. Numerous review articles have summarized the purported differences between apoptosis and necrosis, often presenting the differences as nearly absolute. In addition to the cytological differences between cells undergoing apoptosis or necrosis, such articles usually indicate that apoptosis affects single cells while necrosis affects groups of cells, that necrosis elicits inflammation while apoptosis does not, and that apoptosis is physiological while necrosis is pathological. Most review authors indicate that apoptosis and necrosis are morphological diagnoses, but many scientists use nonmorphological methods to distinguish between the two processes, which they frequently study in cell cultures. Those whose studies include examination of histological sections often use the TUNEL technique, sometimes mistakenly believing it distinguishes between apoptosis and necrosis. Such strict delineations between apoptosis and necrosis have caused growing confusion and consternation among pathologists, particularly toxicologic pathologists, who recognize that cells displaying the characteristic cytological features of apoptosis often occur in settings contrary to the published accounts. For example, in animals subjected to toxicants, cells with apoptotic cytological features can occur in clusters or groups (sometimes in large numbers) as a patho-

logical finding. Conversely toxicologic pathologists have long recognized "single cell necrosis" as a pathological finding. Reports linking apoptotic injury with inflammation have also appeared (Zychlinsky and Sansonetti, 1997).

In what may become a landmark article, Majno and Joris (1996) provide a new paradigm. They point out that the term necrosis has always been used by pathologists to designate the presence of dead tissues or cells in a living organism. They also explain that necrosis is the sum of changes occurring in the cells after they have died regardless of the prelethal process. One process leading to cell death is apoptosis (cell injury characterized by cytoplasmic shrinkage and karyorrhexis). As a counterpoint to apoptosis, they introduce the term "oncosis" (cell injury characterized by cytoplasmic swelling and karyolysis). Oncosis comprises the prelethal changes leading to ischemic or coagulation necrosis. Such prelethal changes were previously known as cloudy swelling or hydropic degeneration. Thus, necrosis may be either oncotic or apoptotic in origin. This paradigm also allows for other types of cell death, such as autophagocytic cell death (Zakeri *et al.*, 1995) or types yet to be described. After a period of intense confusion, Majno and Joris' paradigm allows us to reappropriate the term necrosis as a general term for dead cells *in situ*.

### THE RECOMMENDATIONS: NECROSIS IS THE DIAGNOSIS

The Committee recommends that when dead cells are observed in a histological section, necrosis is the appropriate primary diagnosis. If the cells have an apoptotic cytomorphology, the use of the modifier "apoptotic" is appropriate, i.e., *apoptotic necrosis* is an appropriate diagnosis. (Note: Majno and Joris also recommended this.) This diagnosis may apply even when apoptotic cells appear in clusters or are accompanied by inflammation. When the dead cells or tissues have histological characteristics indicative of oncotic cell injury, *necrosis* with traditional modifiers such as coagulative, ischemic, etc. will be easily understood and are appropriate. In some situations, however, it may be necessary to add the adjective *oncotic* to the diagnosis to distinguish a lesion's

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appearance from apoptotic necrosis. There are, of course, lesions where both types of cell death are present and this may be indicated by *mixed oncotic and apoptotic necrosis* or some similar string. When there is uncertainty that the observed cells are actually dead, *degeneration* or *degeneration/necrosis* may be used with the appropriate modifier (oncotic, apoptotic, or mixed).

There are lesions where it is not possible to determine from the histological section whether the cells died by a process of apoptosis, oncosis, or something else. In such cases the unmodified term necrosis or "necrosis, n.o.s." may be appropriate. This is often true in the central nervous system where dead neurons typically have a shrunken eosinophilic appearance regardless of how they died. Regardless of the morphological diagnosis used in incidence tables, and especially in cases of compound-related changes, the Committee recommends that the report narrative describe the types of cell injury and death observed and place the lesion in context so that readers of the report obtain a clear understanding of what was seen. At this time in the history of cell biology it is particularly important for us to accurately and clearly communicate the types of cell injury and death that occurred.

The term oncosis has potential liabilities to toxicologic pathologists. Although its root meaning is "swelling," it can be confused with neoplastic disease. Indeed, some medical dictionaries define oncosis as pertaining to neoplastic disease.

Although the majority of the STP Committee does not like the term oncosis, we have no ready alternative to describe the process of cell injury characterized by swelling. Oncosis is already gaining acceptance among experimental pathologists and so we reluctantly accept it. We recommend, however, that the noun oncosis be avoided, when possible, in favor of the adjective "oncotic" used as a diagnostic modifier.

Until these recommendations take hold outside our specialty, it will be necessary for all of us to extend some effort to elucidate their meanings to toxicologists, cell biologists, regulators, pharmacologists, and pathologists in other specialties.

The Committee invites your comments. Please submit them in writing to one of the committee members within 1 month after this publication or to Stuart Levin at [stuart.levin@monsanto.com](mailto:stuart.levin@monsanto.com).

#### REFERENCES

- Majno, G., and Joris, E. (1996). Apoptosis, oncosis, and necrosis: An overview of cell death. *Am. J. Pathol.* **146**, 3–15.
- Zakeri, Z., Bursch, W., Tenniswood, M., and Lockshin, R. A. (1995). Cell death: Programmed, apoptosis, necrosis or other? *Cell Death Differ.* **2**, 87–96.
- Zychlinsky, A., and Sansonetti, P. (1997). Apoptosis as a proinflammatory event: What can we learn from bacteria-induced cell death? *Trends Microbiol.* **5**, 201–204.