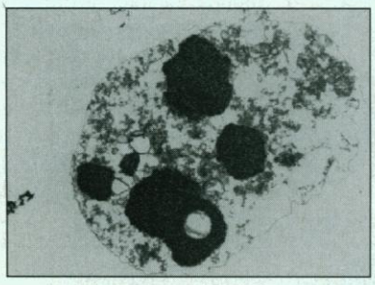
Apoptosis

The topic of this special section is one of the hottest in biology: apoptosis, the highly orchestrated form of cell death in which cells neatly commit suicide by chopping themselves into membrane-packaged bits. Apoptosis, also known as programmed cell death, has caught the imagination of researchers worldwide. There's good reason for the interest. As noted in the Editorial on page 1283, apoptosis is critical to the health of many organisms, needed to sculpt the nervous system during development and to maintain the normal functioning of the immune system. And when apoptosis malfunctions, the results may be dire: cancer and autoimmune diseases when there is too little apoptosis, and possibly stroke damage or the neurodegeneration of Alzheimer's disease when there is too much. Because of the importance of apoptosis and the recent explosive progress toward dissecting its molecular basis, we have asked some of the leaders in the field to describe the insights gained from these advances, point out the questions that remain unanswered, and discuss the directions that new research should take.



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Ashkenazi and Dixit start by describing the signaling pathways that tell cells when it's time to die. They begin with the so-called "death receptors" on the cell membrane and walk us through an area that has been fraught with controversy this past year but may finally be sorting itself out. It concerns exactly how the signals are transmitted from the various receptors, eventually resulting in the activation of protein-splitting enzymes called caspases. Thornberry and Lazebnik delve into the world of the caspases themselves, describing the "caspase cascade" that ultimately dissembles cells. Although they are not part of this special section, this issue also contains a Perspective (p. 1298) and a Report (p. 1352) that deal with how the prototype caspase, called CED-3, becomes activated.

Green and Reed take a look at another important player in the death pathway, the mitochondria. Conventionally considered the cell's powerhouses, these small organelles are intimately entwined in numerous death pathways. For example, by releasing cytochrome c into the cytoplasm, the mitochondria can contribute to caspase activation. Members of the Bcl-2 clan help regulate this mitochondrial activity and have other roles in apoptosis as well. As Adams and Cory describe, this large family of proteins includes some of the cell's most potent death signals as well as some of its premier protectors of cell survival. Among the latter are Bcl-2 itself, originally discovered as the protein made by an oncogene that can, when activated, contribute to cancer development.

In addition to being triggered through death receptors, apoptosis can also be initiated by a variety of insults that can damage DNA, including ultraviolet- and x-irradiation and chemotherapeutic drugs. Proteins that sense DNA damage and help trigger apoptosis also affect the cell cycle—stopping cell division so that the damage can be repaired or making the decision that the damage has gone too far and the cell must die. Evan and Littlewood pull together what we know about how these regulators operate and about how their malfunction might lead to cancer by allowing cells to proliferate when they should either self-destruct or temporarily stop dividing.

Finally, the two stories in the News component of the special section describe evidence that the opposite problem—apoptosis occurring when it shouldn't—may contribute to brain neuron loss in stroke and Alzheimer's disease. If so, it might be possible to develop new therapies for the conditions that work by inhibiting apoptosis. Because the caspases are central to most cell death programs, they present an attractive target for such therapeutic interventions.

–LINDA J. MILLER AND JEAN MARX

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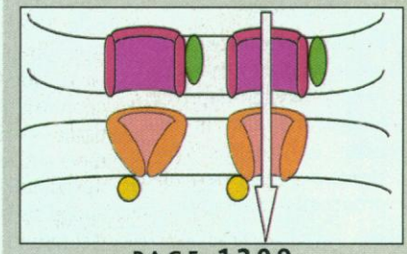

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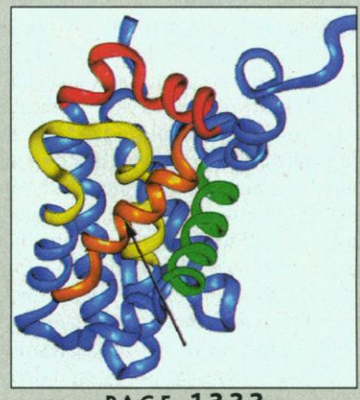

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See also the Editorial on page 1283, the Perspective on page 1298, and the Report on page 1352.

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