

“Cell Deaths in Normal Vertebrate Ontogeny,” by Alfred Glücksmann

The review article “Cell Deaths in Normal Vertebrate Ontogeny” (abbreviated as “Cell Deaths”) was published in *Biological Reviews* of the Cambridge Philosophy Society in 1951. The author, Alfred Glücksmann, was a German developmental biologist then working at the Strangeways Research Laboratory, Cambridge, England. In “Cell Deaths,” Glücksmann summarizes observations about cell death in normal vertebrate development that he had compiled from literature published during the first half of the twentieth century. “Cell Deaths” emphasizes the frequent occurrence of cell death in various locations and stages of development, and suggests that cell death functions as a crucial mechanism in integrating cells into tissues and organs in normal vertebrate ontogeny.

Glücksmann structures his review into seven sections, four of which (II, III, IV, and V) constitute the bulk of the paper. After a brief introduction, section II outlines the major morphological changes observed in cell death. In Section III, he classifies seventy-four embryonic cell death observations recorded in the literature and divides them into nine groups according to timing and location in development. In section IV these phenomena are regrouped into three categories according to the developmental functions they perform. In the next section, the author evaluates existing hypotheses and gives his own interpretations about why cell death occurs in developing embryos. The article ends with a numerically listed recapitulation of his major points.

In the first several decades of the twentieth century it was difficult for embryologists to accept that cells could die in actively growing regions of developing embryos. The simultaneous existence of death and vigorous growth sounded paradoxical, if not downright impossible. As such, dying cells were sometimes misinterpreted as special metabolites secreted by dividing cells. Perhaps to address these philosophical qualms and experimental confusions, Glücksmann asserts that there is a wide existence of cell death in embryological processes and he rebuts the hypothesis that they are mitotic metabolites. He devotes the first major section of his paper to a description of the common morphology observed in cell death during normal vertebrate development.

Glücksmann divides cell death processes in normal development into three stages, according to the morphological changes in the cell nucleus. He calls the first stage chromatopycnosis, in which the chromatic components and the non-chromatic materials of the nucleus separate. Specifically, the chromatic materials precipitate and coalesce into aggregates that Glücksmann calls granules. These aggregates eventually unite into a single mass, while the non-chromatic portions assemble into interconnected vacuoles. Glücksmann identifies the second stage of cell death as hyperchromatosis of the nuclear membrane. Here, the single chromatic mass shrinks and migrates to the edge of the vacuole formed by non-chromatic materials and the volumes of both cytoplasm and nucleus gradually decrease at this stage. In the third stage, chromatolysis, the original chromatic single mass loses its affinity for nuclear stains such as Feulgen stain, and eventually deforms and disappears. Glücksmann points out that these three stages of cell death can occur in isolated cells and in cells that have phagocytosed dying cells. He completes this section by adding other morphological variations observed in cell death that deviate from his general description.

As mentioned above, in section III, “The Incidence and Localization of Cell Degenerations during Normal Vertebrate Development,” Glücksmann lists seventy-four observations of cell death in development in the literature and groups them into nine categories according to the timing and location of occurrence. The categories include cell deaths in embryogenesis, formation of nervous system, sense organs, epidermis and transient ectodermal structures, digestive tract, respiratory tract, vascular system, and locomotory apparatus. The cell death data also include species, tissue site, and

the developmental process concerned. For example, Glücksmann notes that cell death had been detected in frog retina during differentiation of the three layers of the retina.

Glücksmann also discusses existing studies in each category of cell death. He spends much ink commenting on cell death in the development of the nervous system and sense organs, integrating research results obtained in his own studies at Strangeways. One example is a discussion about the role of cell death in forming the vertebrate optic cup. In tadpole embryos, cell death had been detected when the optic vesicle was undergoing invagination, resulting in the formation of the optic cups. Researchers hypothesized that in shaping optic cups, either the dying cells induced the movement of optic vesicles, or the invagination movements caused the cell death. Glücksmann regards these assigned causal relations between cell death and cell movement as overly simplistic and deterministic. He argues instead that both cell death and cell movement contribute to the shaping of the optic cup, therefore they are more likely to be integrated by a regulation mechanism that controls both processes, which he calls differentiating impulse.

In section IV, "Classification of Cell Degenerations According to Their Developmental Functions," Glücksmann attempts to arrange cell deaths according to function. He assigns them to three new categories: morphogenetic, histiogenetic, and phylogenetic degeneration. Morphogenetic degeneration encompasses cell death that serves to shape certain forms of organs or tissues, such as the death of central cells in the formation of lumina in solid glands, such as the liver. Glücksmann uses the term histiogenetic degeneration to express his view that some cells die due to their failure to respond to differentiating signals. This is because the cells are already specialized in another direction. He regards the partial resorption of Wolffian ducts (a pair of organs that in males develop into a system connecting the testis and the prostate) in female mammals as an example of histiogenetic degeneration. Phylogenetic degeneration, Glücksmann's third category, characterizes cell deaths in the involution of vestigial organs and those in the regression of larval organs. Possible functions for some incidences of cell death, however, were more difficult to identify. Glücksmann therefore leaves eight of the occurrences of cell death listed in the previous chapter ungrouped. Most of these unclassified cell deaths occur in early embryogenesis.

In section V, "Discussion," Glücksmann addresses the possible causation of cell death in developing embryos. He first assesses a hypothesis advanced during the 1920s by Max Ernst, a biologist working at Heidelberg University, Germany. Ernst suggested that embryonic cells die either because they exhaust their endogenous life energy or because they are subjected to nutritional disruption. Glücksmann rejects Ernst's ideas, reasoning that embryonic cells could always rejuvenate their life energy through cell division and that the majority of embryo cell deaths had been shown to be independent of fluctuations of nutrition in physiological conditions. Glücksmann then hypothesizes that cell death might result from differential responses of a group of cells to a developing stimulus, which he called a differentiating impulse expanding over a field of cells. He suggests that some cells respond to such stimuli and participate to form the final organ, while others react slowly or are unable to respond. These cells then enter a stage of terminal differentiation, age, and die. Glücksmann nevertheless concedes that his hypothesis could not adequately explain the cell death that precedes changes in form, since any unchanged structure would strongly indicate the absence of a differentiating stimulus.

In "Cell Deaths," Glücksmann expresses hope that his review will encourage his peers to study cell death as a mechanism of tissue and organ formation. His efforts did not, however, elicit much of a response from the embryological community. With time, Glücksmann redirected his research to sex determination and hormonal effects on cancer. In the 1970s, three pathologists working at the University of Aberdeen, John Foxton Ross Kerr, Andrew H. Wyllie, and Sir Alastair Robert Currie, rediscovered Glücksmann's "Cell Deaths" while they were investigating cell death phenomena in tumors and organ atrophy. They found that the type of cell death described by Glücksmann was surprisingly similar to their own findings. In their 1972 article "Apoptosis: A Basic Biological Phenomenon with Wide-Ranging Implications in Tissue Kinetics," Glücksmann's article "Cell Deaths" serves as a cornerstone reference. In the 1990s, when research on apoptosis flourished, Glücksmann's "Cell Deaths" began to be widely cited as a classic review of early research on cell death in development.

Sources

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