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NINETEENTH CENTURY RESEARCH ON CELL DEATH

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This paper reviews research on cell death in the 19th C. The first report of cell death was by Vogt in 1842, which was remarkably soon after the establishment of the cell theory by Schleiden and Schwann between 1838 and 1842. Initial studies on cell death, including that of Vogt, focused on its occurrence in metamorphosis (Vogt, 1842; Prévost and Lebert, 1844; Weismann, 1863–1866) or in blatant pathology (Virchow, 1858), but as histological techniques improved it was found to be involved in more subtle roles in numerous situations including endochondral ossification (Stieda, 1872), ovarian follicle atresia (Flemming, 1885), cell turnover (Nissen, 1886), the wholesale loss of a population of sensory neurons in fish (Beard, 1889), and the naturally occurring histogenetic death of myocytes (Felix, 1889) and neurons (Collin, 1906). The current categorization of cell death into about three main morphological types has 19th century roots in that apoptosis was well described by Flemming (1885), who called it chromatolysis, and various authors including Noetzel (1895) proposed a threefold classification. This article is part of a Special Issue entitled "Apoptosis: Four Decades Later".

***Key Words*: apoptosis, cell death, history, necrobiosis, necrosis.**

Over the last twenty years the field of cell death has become one of the most intensely researched fields in biology. The fact that large numbers of cells die in many tissues in normal development, and in numerous pathologies, is now too well known to need to be argued, and its importance is universally recognized. We here discuss the origins of this research in the 19th century, when the importance of the phenomenon was far from clear [1, 2]. We point out that the currently important categorization of cell death into apoptosis and other types has 19th century roots.

THE CONCEPTUAL AND TECHNICAL CONTEXT OF 19TH CENTURY RESEARCH ON CELL DEATH

The study of cell death required an understanding of the nature of cells and the technology to visualize them. Even though cells had been observed in biological tissues before the end of the 17th C, and early compound microscopes were able to resolve small cells, the detailed microscopic visualization of cellular contents only became possible after the middle of the 19th C. This required improvements in both microscope design and tissue preparation. Two of the most important 19th C advances in microscope design were Joseph Lister's development in 1830 of a technique for reducing chromatic aberration by combining several appropriately placed weak lenses, and Ernst Abbe's elucidation in 1872 of his "sine condition", permitting calculations for optimizing microscopical resolution [3]. As a result of these and other improvements, microscopic resolution improved from about 1 μm in 1840 to about 0.25 μm in 1870 [3].

As microscopic resolution improved, tissue preparation became a limiting factor. Before about 1860, microscopical observations of biological tissues were performed mostly on squashed or hand-cut preparations of fresh, unstained tissues. Methods of fixation started to be introduced since the 1830s, with Jacobsen's proposal of chromic acid as a "hardening agent" in 1833, then Hannover's use of chromium trioxide in 1840, followed by other agents including acetic acid-ethanol and "osmic acid" (osmium tetroxide) in the 1850s and 1860s [4]. Also, primitive microtomes and staining methods had been tried since the 18th C [4], but it was only in the 1880s that techniques for fixing, embedding, sectioning and staining came into regular use.

Despite these limitations, as early as 1805 Lorenz Oken made his (now famous) statement that "all living organisms originate from and consist of cells", but it was only after the publications in 1838–1842 of Schleiden and Schwann [5–7] that the cell became widely accepted as the fundamental unit of all living tissue. It required the further insight of Virchow [8] to add in 1858 that all cells come from preexisting cells.

THE DISCOVERY OF CELL DEATH

Cell death was first described by Carl Vogt in his monograph on the development of the midwife toad, which was published in 1842 [9], which was remarkably soon after the establishment of the cell theory by Schleiden and Schwann. Influenced by Schwann, whom he mentions, Vogt came to his research with specifically cellular questions in mind, and he made use of the crude microscopy that was then available, without fixation, tissue sectioning or staining, to examine individual cells. One of his cellular questions was whether the disappearance of the anuran notochord during metamorphic climax, and its replacement by the vertebrae and the base of the skull, was due to a transformation of the existing notochord cells into cartilage, or to the elimination of these cells and their replacement by new ones. He correctly [10] established the latter hypothesis, stating that the existing

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cells were resorbed and replaced by the formation of new cells from the neighboring cartilage. He also showed that cell death occurred among the cartilage cells. He did not specifically use the term cell death, but this idea was implied by his description of the cells being resorbed (e.g. p86). The term cell death (Zelltod) was rarely used during the 19th C, although Hertwig had a chapter entitled "Degeneration und Tod der Zelle (Necrose)" in his 1898 book on cells and tissues [11]. Until words were invented for particular types of cell death (e.g. chromatolysis), the concept of cell death was generally conveyed by the use of words with a tissue-level meaning applied to the destruction of cells (in German: Histolyse, Degeneration, Necrose, Involution, Rückbildung (regression)).

Although of German origin, Vogt did this research in Neuchatel, in French-speaking Switzerland, and within two years the "absorption" of cells in the notochord had been confirmed in frogs by Jean-Louis Prévost and Hermann Lebert [12] working in nearby Geneva. However, their observations seem to have been at an earlier stage of development, before the full scale degeneration of the notochord had begun.

Neither Vogt, nor Prévost, nor Lebert, nor anybody else was particularly interested in these initial observations of cell death, and they were not followed up. Vogt had many other interests (Fig. 1), as did Prévost (who founded the first outpatient hospital in Europe) and Lebert (a clinician, pathologist and comparative anatomist), and the time was not ripe for a serious study of cell death. Nevertheless, from gross observations of damaged or degenerating tissues pathologists came to realize that cell death must be occurring, as was first argued in 1858 by Virchow in Lecture XV of his Cellular Pathology [8]. But the next major advance came from the study of metamorphic flies and other insects.

Fig. 1. Bust of Carl Vogt (1817–1895) in front of a building of the University of Geneva (Parc des Bastions). Vogt became famous because of his wide-ranging scientific publications on geology, zoology and physiology, and was very active in politics in both Frankfurt and Geneva. Despite being the first person to detect cell death, he was never particularly interested in this phenomenon, and never to our knowledge referred to it apart from in his 1842 publication

CELL DEATH IN METAMORPHIC INSECTS

The obvious implication of Vogt's research, that cell death must underlie tissue regression in metamorphosis, was not followed up until the 1860s, when August Weismann, working in Freiburg-im-Breisgau (Baden-Württemberg, Germany), studied microscopically the embryonic [13] and postembryonic [14] development of three species of diptera, observing widespread "Histolyse" during pupation. Importantly, he showed that most of the larval tissues were completely destroyed by massive cell death, but that some organs, including the central nervous system, were profoundly modified by the histolysis without being destroyed. He attempted to describe the cytological appearance of the dying cells, and used the term fatty degeneration. This term — "fettige Entartung" — had been used by pathologists such as Virchow to refer to situations in which fat accumulated in the degenerating organs, leaving open the question of whether the fat was between the organ's cells or within them. Weismann used the term in the latter sense, because he could detect numerous vacuoles, and assumed them to be filled with lipidic material, although in reality they were probably autolysosomes [15]. Weismann then gave up his histological research on flies because of an eye disease, and devoted himself mainly to the theoretical studies on heredity for which he is now most famous, but others followed up his research and the relevant papers on insect metamorphosis from 1870 to 1882 are summarized in Table. These early authors had little to say on the causes of the cell death, but Kowalevsky [16, 17] and van Rees [18], inspired by the work of Metchnikoff on the muscles of metamorphic toads (see below), suggested that it was promoted by amoeboid phagocytic cells (i.e. macrophages) that they observed in the tissue. Subsequent 19th C authors contested this view [19] and the subject is still not entirely clear. The main role of macrophages in relation to cell death is generally considered to be the clearance of dead cells, but there is evidence that macrophages can in some cases induce the cell death [20].

Table. Early studies of cell death in metamorphic insects

Year	Author, ref.	Tissue	Species
1864, '66	A Weismann [14,65]	Various	Diptera
1869	M Ganin [66]	Various	Diptera
1870	BT Lowne [67]	Various	Blow fly
1876	C Chun [68]	Intestine, glands	Bee, butterfly
1876	FE Helm [69]	Silk glands	Silk moth
1882	H Viallanes [55]	Various	Fly

METAMORPHIC AMPHIBIA

In metamorphic amphibia, the role of cell death in tissue regression was understood somewhat later than in insects. As early as 1866, Eberth [21] observed what appear to have been pyknotic cells in the dermis of the regressing tadpole tail, and even raised the possibility that these were dying cells, but rejected his own correct hypothesis. Likewise Goette, in his initial (1869) publication on regressing tissues [22], failed to recognize the cell death, but six years later [23] described cell death during metamorphosis in the notochord (confirming Vogt, whom he cited) and argued that it must occur in various tissues of the regressing tail and gills and elsewhere. This failed, however, to arouse interest until the subject was revived by Metchnikoff, Mayer and Barfurth in the 1880s.

In 1883, Metchnikoff, working in the isolation of his own private laboratory at Messina, Sicily, inferred the occurrence of histolysis in regressing muscles

of metamorphic toads from the presence of numerous phagocytes that could sometimes be seen to contain fragments of striated (so presumably muscular) tissue as well as the still identifiable debris of axons [24]. Three years later, Mayer, working at the German University in Prague, studied ovoidal, transversely striated bodies in muscular tissues of tadpoles and young frogs, and came to the conclusion that these "Sarkoplasten" (as others had called them — the word means myoblasts) were in fact the products of muscle degeneration [25]. He argued that the "Sarkolyten" (as he re-named them) could not be myoblasts, because they occurred even in well differentiated muscle, and favored their identification as degeneration products because they were particularly numerous in regressing tail, and could sometimes be identified in other cells (now known to be phagocytes). In 1887 Barfurth confirmed this research using tissues that had been embedded and sectioned, and provided impeccable drawings of dying cells in numerous tissues including skin, capillaries, notochord and spinal chord [26]. In the remaining years of the 19th C this field of research became popular, being extended by numerous authors including Noetzel, Looss and Bataillon [1].

The research of Metchnikoff and Mayer stimulated a major debate on the causes of the cell death underlying metamorphic tissue regression. Many authors shared an assumption going back at least to the 1840s (e.g. ref. [12]) that the regression resulted from ischemia due to the occlusion or regression of capillaries [27]. Barfurth accepted this interpretation and attributed the occlusion to the effects of a reduced "trophic" influence from the nervous system due to disuse of the tail once the limbs appeared [26]. This view is now known to be false, but the notion of (purely anterograde) trophic influences was very fashionable in the middle and late 19th C, being championed by no less than Jean-Martin Charcot [28]. The influences were believed to be mediated by a distinct class of "trophic nerves" with special trophic functions in the autonomic nervous system. This view was abandoned when it was found that removal of the autonomic nervous system did not have the predicted effects [1, 28], but the notion of neurotrophic effects (now known to be both anterograde and retrograde) was revived following the discovery of the neurotrophins and other classes of neurotrophic factors, and this is now a major field of neuroscience [29].

CELL DEATH IN THE ABSENCE OF METAMORPHOSIS

Even though the earliest studies of (nonpathological) cell death were in metamorphosis, several publications in the 1870s reported cell death during non-metamorphic development in situations where gross tissue transformations are known to occur. The first of these focused on the death of chondrocytes during endochondral ossification [30]. This was followed Flemming's study of cell death during atresia of the membrana granulosa of Graafian follicles. The periodic degeneration of the granulosa was already known in the 1870s, and Wagener understood in 1879 that this implied cell loss [31], but Flemming's 1885 study [32] was important because he developed improved histological techniques (fixation with a mixture of chromic acid, osmium tetroxide and acetic acid, and staining with safranin) and was therefore able to provide a detailed description of the dying cells, which he described as "chromatolytic" as is discussed below. Two later studies reported the wholesale loss in fish [33] and skate [34] of a population of primary sensory neurons that are now called the Rohon-Beard neurons are now known to be eliminated in lampreys and amphibia as well as in fish.

The above studies concerned the elimination of entire populations of cells, but much naturally occurring cell death involves the loss of only a proportion of the cells, and many of their neighbours persist. Such partial loss occurs in adults in tissues subject to cell turnover, and in most or all tissues at particular moments in development.

Cell turnover is cell death compensated by proliferation, and is the means of self-renewal in many tissues including epidermis, intestine, lung, blood and most or all glands [35]. This is a major phenomenon in most vertebrate and invertebrate species including humans, and in each of us the mass of cells lost by death — and replaced by proliferation — in one year through cell turnover is equal to almost our own weight [35]. Despite the importance of this turnover, and the obvious need of a means of cell removal to compensate proliferation (as Gräper argued [36]), this cell death was not detected until 1886 because of technical difficulties. The problem was that only a small proportion of the cells in a tissue are recognizable morphologically as dying or dead cells at a given moment, so detection of the cell death was more difficult than the detection of massive cell death during gross tissue loss or transformation, and had to await technical improvements in the 1880s. The first person to recognize this cell death was Nissen in 1886, who used Flemming's fixative and a hematoxylin nuclear stain, enabling him to detect scattered dying cells in mammary glands of lactating dogs, rabbits and cats [37]. The morphology of the dying cells resembled that observed by Flemming one year earlier, so Nissen adopted Flemming's terminology, describing the dying cells as "chromatolytic". It is now known that this cell loss during lactation is minor in comparison with the cell death that occurs in the regressive phase after lactation, but Nissen did not study this. Four years later, Heidenhain reported similar observations of chromatolytic cells in various glands of adult newts [38].

NATURALLY OCCURRING DEATH OF POSTMITOTIC CELLS DURING DEVELOPMENT

It is well known that postmitotic neurons in vertebrates, including mammals, undergo a phase of massive cell death, during the period of synaptogenesis,

reducing the number of neurons in a given population by about 50% (on average, but percentages range from 0 to 70% or more). The raison d'être for this remarkable irreversible reduction is a matter of debate, but all agree that it is related to the competition between neurons to form, and probably to receive, connections. The most widely accepted hypotheses are that the neuronal death serves to match the numbers of neurons with the size of their axonal target territory, or to eliminate neurons whose connections are in some sense aberrant [39, 40]. Clues to the existence of this neuronal death were provided by Barfurth (in 1895), and by Capobianco and Barbieri (both in 1905) [1], but it was first clearly stated and demonstrated by a French doctoral student, Rémy Collin, who reported in 1906 the death of motoneurons and spinal ganglion cells in chick embryos [41, 42]. We have argued elsewhere that Collin realized the importance of this phenomenon, and its probable relevance to all vertebrates [1], but he did not pursue this theme in later life.

Postmitotic myocytes in striated muscle resemble neurons in that they undergo a similar phase of cell death during development, at the time when they are receiving neural connections. This has not been so well studied as neuronal death, but the survival of the muscle cells seems to depend on the receipt of connections [43], as was implied by the very early observation that muscle cells are absent in fetuses that lack the relevant part of the spinal cord [44]. The first person to describe this cell death was Walther Felix, who reported in 1889 his observations on skeletal muscles of human fetuses [45]. He identified dying cells, resembling the sarcolytes of Mayer and Barfurth, in muscles that were beginning to receive innervation. Furthermore, he argued astutely that innervation appeared to initiate a morphological change in muscle fibers, and that those which died had never made that change, implying that the receipt of innervation prevented muscle fiber death [45].

HISTORICAL ROOTS OF THE APOPTOSIS-NECROSIS DISTINCTION

Virchow [8] distinguished between two different degenerative phenomena, which he called *necrosis* and *necrobiosis*. He argued that necrosis was a passive pathological event, whereas "Necrobiosis is death brought on by (altered) life, a spontaneous wearing out of living parts, the destruction and annihilation consequent on life, natural as opposed to violent death (mortification)" [8, 46]. Virchow was not referring to individual cells, but to degenerating tissues, and he envisaged even necrobiosis in pathological situations, but the notion that active natural processes could lead to cell death was prefigured by his ideas. Moreover, the term necrobiosis did subsequently come to mean naturally occurring cell death [41].

Virchow's necrosis-necrobiosis dichotomy resembles to some extent the modern one between *necrosis* and *apoptosis*, according to which all cell death has been claimed to be either necrosis, occurring in grossly pathological situations, or apoptosis, occurring in physiological situations but occurring also in mildly pathological ones [47]. This is now held to be only partly true, because as least three types of cell death can occur even in normal development [15], but the apoptosis-necrosis distinction is still important.

At the cellular level, the identification of different morphological types of cell death had to await the improvements in histology introduced in 1885 by Flemming, as mentioned above, and it is he who first identified, in the granulosa of ovarian follicles, during their cyclic atresia, the type of cell death that is now called apoptosis [32]. He was able to describe, rather clearly, the dying granulosa cells as showing striking changes in the nucleus, which had ill-defined borders but contained several lumps that were heavily stained (with safranin or gentian violet); these were sometimes spheroidal and sometimes took the form of "half-moons" at the nuclear membrane (Fig. 2). The cytoplasm was almost normal, being unstained but apparently homogeneous apart from the presence of tiny empty vacuoles that Flemming considered to be fat droplets. He coined the word *chromatolytic* for this type of cell death, because the nuclear chromatin appeared to be disintegrating, and the term was quite widely used in the late 19th and early 20th centuries in studies of development [48], adult tissue turnover [36, 38], or various pathologies including breast cancer [49]. However, the usage has changed and *chromatolysis* now usually refers to the dissolution of Nissl bodies in the cytoplasm of neurons in response to axotomy, ischemia or other insults.

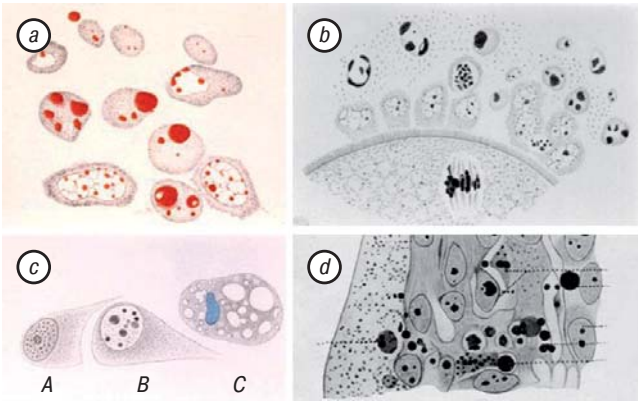

Fig. 2. Early drawings of dying cells, which would now probably be considered apoptotic. *a*, *b* — safranin-stained sections from rabbit ovarian follicles, published by Flemming in 1885 [32]. *a* — epithelial cells, of which the two with the largest nuclei are normal, but the rest are in various stages of chromatolysis. *b* — part of the ovule (below) and adjacent epithelium (above). In the latter, just over half the cells are chromatolytic. *c* — Hematoxylin-alum stained section through a spinal ganglion in a metamorphic frog (Rana esculanta), published by Noetzel in 1895 [48]: *A* — unaltered ganglion cell; *B* — ganglion cell with about 10 chromatin spheres in an enlarged nucleus; *C* — ganglion cell with a shrunken nucleus (darker gray, blue in original) and numerous vacuoles in cytoplasm. *d* — transverse section through spinal cord of 6 day chick embryo, showing dying and healthy neurons in ventral horn, published by Collin in 1906 [41]: *Nd* — degenerating neuroblast, *Nn* — normal neuroblast, *Sb* — white matter, *Mn* — nuclear membrane, *Spl* — free chromatic balls (terminology of Collin, translated)

The modern usage of the word *necrosis* as a type of cell death [47] was contested by Majno and Joris [46], who pointed out that the word has traditionally been used to refer to gross tissue changes occurring secondarily to the cell death itself and occurring much later. They proposed that necrotic cell death involving swelling should be called *oncosis*, a term introduced by von Recklinghausen in a monograph that was published posthumously in 1910 [50]. This alternative term is sometimes used by pathologists but has not been widely adopted.

The word *apoptosis*, which in Greek means the "dropping off" of petals or leaves from plants or trees, has likewise undergone a change of meaning in relation to cell death, because it was initially used, by Hippocrates, for what we now call gangrene [51]. Ironically, gangrene is one of the situations to which Virchow most commonly applied the term necrosis.

MORE THAN TWO TYPES OF CELL DEATH

The existence of more than two types of cell death is currently a matter of debate, but the most widely held view is that there are three main morphological types: type 1, apoptosis; type 2, autophagic cell death; and type 3, which includes necrosis as well as other subtypes resembling mild necrosis [15, 52, 53]. There may be additional types in special situations, and there is a recent tendency to emphasize biochemical rather than morphological criteria for categorizing cell death [54].

In the 19th C, the idea that there might be several distinct types of cell death has its roots in the diversity of early descriptions. For example, the descriptions of *fatty degeneration* by Weismann [14], of *coagulation necrosis* by Weigert and Connheim around 1877 [46], and Flemming's *chromatolysis* [32] were all different. The first explicit claim of multiple cell death types was Viallanes [55], who studied the metamorphosis of various insects and proposed that the destruction of tissues could take place in one of three ways. The details of his proposal have not been confirmed, but several subsequent 19th C authors continued to explore the idea of multiple types [1]. For example, Noetzel claimed that there were three kinds of cell death in spinal ganglia of metamorphic frogs and toads: 1) cell death involving the appearance of heavily stained chromatin spheres in a pale nucleus; 2) nuclear decay without chromatin granules; 3) nuclear shrinkage [48].

The notion of autophagic cell death was hinted at ambiguously in 1892 by Metchnikoff [15], and then in 1898 by de Bruyne, who went so far as to introduce the term "autophagocytose musculaire" [56]. However, he appears not to have envisaged autophagy in the modern sense but rather the removal of cellular debris by *other* cells of the same tissue. The discovery of autophagy and autophagic cell death in the modern sense had to await the invention of electron microscopy [15].

BEYOND THE 19TH CENTURY

As is mentioned above, interest in cell death developed only slowly following its discovery in 1842, but by the last decade of the 19th century it had come to be recognized as an important subject. By the early years of the 20th century the subject was less dominated by German-language publications, and the 1903 French-language histology text book of Prenant, Bonin and Maillard devoted a ten-page chapter to degeneration and cell death [57], which is more than is found in most modern histogy text books. These authors understood the occurrence of cell death in various transitory structures such as the pronephros and Wolffian body and mentioned cell death in the testicles. Interest in cell death continued in the following years, and the publication by Collin of his discovery of naturally occurring death of motoneurons and spinal ganglion cells in chick embryos followed only three years later [41, 42].

But, despite this general recognition, interest in cell death then gradually declined, and in the 1920s and early 1930s the only group with a sustained interest in the subject was that of E. Kallius in Heidelberg, as is evidenced by the publications of his three doctoral students, Max Ernst, Alfred Glücksmann and Werner Jacobson. However the formation of the Third Reich in 1933 had immediate consequences for cell death research, because Glücksmann and Jacobson were expelled from their jobs the same year and joined the Strangeways Laboratory in Cambridge, England, whose director Honor Fell shared their interest in cell death. A positive consequence of this tragic situation was that Glücksmann and Jacobson began to publish in English, making their publications accessible to a wider audience, and Glücksmann's 1951 review on cell death during development [58] was particularly influential.

The history of cell death research after 1951 has been described by numerous authors [51, 59–64].

REFERENCES

1. Clarke PGH, Clarke S. Nineteenth century research on naturally occurring cell death and related phenomena. Anat Embryol 1996; **193**: 81–99.

2. Cherlonneix L. Recherches sur l'autoinitiation de la mort cellulaire à la fin du XIXe siècle. Gesnerus 2007; **64**: 193–218.

3. Turner GL. Essays on the History of the Microscope. Oxford, England: Senecio 1980.

4. Bracegirdle B. A History of Microtechnique. London: Heinemann 1978.

5. Schwann T. Mikroskopische Untersuchungen über die Übereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen. Berlin: Sander 1839.

6. Schleiden MJ. Grundzüge der wissenschaftlichen Botanik nebst einer methodologischen Einleitung als Anleitung zum Studium der Pflanze. Leipzig: Engelmann 1842.

7. Schleiden MJ. Beiträge zur Phytogenesis. Arch Anat, Physiol wiss Med 1838; 137–76.

8. Virchow R. Vorlesungen über Cellularpathologie in ihrer Begründung auf physiologischer und pathologischer Gewebelehre. Berlin: Verlag August Hirschwald 1858.

9. Vogt C. Untersuchungen uber die Entwicklungsgeschichte der Geburtshelferkröte (Alytes obstetricans). Solothurn: Jent und Gassmann 1842.

10. Fox H. Amphibian morphogenesis. Clifton, New Jersey: Humana Press 1983.

11. Hertwig O. Die Zelle und die Gewebe. Jena: Gustav Fischer 1898.

12. Prévost J-L, Lebert H. Mémoire sur la formation des organes de la circulation et du sang dans les batraciens. Ann Sci Nat, 3e série 1844; **1**: 200–25.

13. Weismann A. Die Entwicklung der Dipteren im Einach beobachtungen an Chironomous spec: Musca vonitoria und Pulex Canis. Z wiss Zool 1863; **14**: 187–336.

14. Weismann A. Die nachembryonale Entwicklung der Musciden nach Beobachtungen an Musca vomitoria und Sarcophaga carnaria. Z wiss Zool 1864; **14**: 187–336.

15. Clarke PGH. Developmental Cell-Death — Morphological Diversity and Multiple Mechanisms. Anat Embryol 1990; **181**: 195–213.

16. Kowalevsky A. Beiträge zur nachembryonalen Entwickelung der Musciden. Zool Anz 1885; **8**: 98–103, 123–8, 153–7.

17. Kowalevsky A. Beitrage zur Kenntnis der nachembryonalen Entwicklung der Musciden. Z wiss Zool 1887; **45**: 542–94.

18. van Rees J. Beitrage zur Kenntnis der inneren Metamorphose von Musca vomitoria. Zool Jahrb Abt Anat Ontog Thiere 1888; **3**: 1–134.

19. Noetzel W. Zur Kenntnis de Histolyse. Arch Pathol Anat 1898; **151**: 7–22.

20. Stefater JA, Ren SY, Lang RA, Duffield JS. Metchnikoff's policemen: macrophages in development, homeostasis and regeneration. Trends Molec Med 2011; **17**: 743–52.

21. Eberth CJ. Zur Entwicklung der Gewebe im Schwanze der Froschiarven. Arch mikrosk Anat 1866; **2**: 490–503.

22. Goette A. Untersuchungen über die Entwickelung des Bombinator igneus. Arch mikrosk Anat 1869; **5**: 90–125.

23. Goette A. Die Entwicklungsgeschichte der Unke (Bombinator igneus) als Grundlage einer vergleichenden Morphologie der Wirbelthiere. Leipzig: Voss 1875.

24. Metschnikoff E. Untersuchungen über die Mesodermalen Phagocyten einiger Wirbeltiere. Biol Zentralbl 1883; **3**: 560–5.

25. Mayer S. Die sogennanten Sarkoplasten. Anat Anz 1886; **1**: 231–5.

26. Barfurth D. Die Rückbildung des Froschlarvenschwanzes und die sogenannten Sarcoplasten. Arch mikrosk Anat 1887; **29**: 35–60.

27. Whitney WU. On the changes which accompany the metamorphosis of the tadpole, in reference especially to the respiratory and sanguiniferous systems. Trans Roy Microsc Soc 1867; **15**: 43–57.

28. Levine JM. Historical-Perspective — the Neurotrophic Theory of Skin Ulceration. J Amer Geriatr Soc 1992; **40**: 1281–3.

29. von Bartheld CS. Axonal transport and neuronal transcytosis of trophic factors, tracers, and pathogens. J Neurobiol 2004; **58**: 295–314.

30. Stieda L. Die Bildung des Knochengewebes: Festschrift des Naturforschervereins zu Riga, zur Feier des Fünfzigjährigen Bestehens der Gesellschaft Practischer Aerzte zu Riga. Leipzig: Engelmann 1872.

31. Wagener GR. Bemerkungen über die Eierstock und den gelben Körper. Arch Anat Physiol, Anat Abt 1879; Jahrgang 1879: 175–200.

32. Flemming W. Über die Bildung von Richtungsfiguren in Säugethiereiern beim Untergang Graaf'scher Follikel. Arch Anat Entwickl 1885: 221–44.

33. Beard J. On the Early Development of Lepidosteus osseus — preliminary notice. Proc Roy Soc Lond 1889; **46**: 108–18.

34. Beard J. The transient ganglion cells and their nerves in Raja batis. Anat Anz 1892; **7**: 191–206.

35. Pellettieri J, Alvarado AS. Cell turnover and adult tissue homeostasis: From humans to planarians. Annu Rev Genet 2007; **41**: 83–105.

36. Gräper L. Eine neue Anschauung über physiologische Zellausschaltung. Arch Zellforsch 1914; **12**: 373–94.

37. Nissen F. Über das Verhalten der Kerne in den Milchdrüsenzellen bei der Absonderung. Arch mikrosk Anat 1886; **26**: 337–42.

38. Heidenhain M. Beitгдge zur Kenntnis der Topographie und Histologie der Kloake und ihrer drusigen Adnexa bei den einheimischen Tritonen. Arch mikrosk Anat 1890; **35**: 173–274.

39. Buss RR, Sun W, Oppenheim RW. Adaptive roles of programmed cell death during nervous system development. Annu Rev Neurosci 2006; **29**: 1–35.

40. Clarke PGH. Neuron Death in the Developing Avian Isthmo-Optic Nucleus, and Its Relation to the Establishment of Functional Circuitry. J Neurobiol 1992; **23**: 1140–58.

41. Collin R. Recherches cytologiques sur le développement de la cellule nerveuse. Névraxe 1906; **8**: 181–309.

42. Collin R. Histolyse de certains neuroblastes au cours du développement du tube nerveux chez le poulet. C R Soc Biol 1906; **60**: 1080–1.

43. Sohal GS, Holt RK. Role of Innervation on the Embryonic-Development of Skeletal-Muscle. Cell Tissue Res 1980; **210**: 383–93.

44. Weber EH. Über Abhangigkeit der Enstehung der animalischen Muskeln von der animalischen Nerven. Arch Anat Physiol wiss Medizin 1851: 548–66.

45. Felix W. Über Wachsthum der quergestreiften Muskulatur nach Beobachtungen am Menschen. Z wiss Zool 1889; **48**: 224–59.

46. Majno G, Joris I. Apoptosis, Oncosis, and Necrosis — An Overview of Cell-Death. Amer J Pathol 1995; **146**: 3–15.

47. Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. Int Rev Cytol 1980; **68**: 251–306.

48. Noetzel W. Die Rückbildung der Gewebe im Schwanz der Froschlarve. Arch mikrosk Anat 1895; **45**: 475–512.

49. Stobe H. Zur Kenntnis verschiedener cellularer Vorgange und Erscheinungen in Geschwulsten. Beitr pathol Anat 1892; **11**: 1–38.

50. von Recklinghausen F. Untersuchungen über Rachitis und Osteomalacie. Jena: Verlag Gustav Fischer, 1910.

51. Diamantis A, Magiorkinis E, Sakorafas GH, Androutsos G. A Brief History of Apoptosis: From Ancient to Modern Times. Onkologie 2008; **31**: 702–6.

52. Penaloza C, Lin L, Lockshin RA, Zakeri Z. Cell death in development: shaping the embryo. Histochem Cell Biol 2006; **126**: 149–58.

53. Clarke PGH. Apoptosis versus necrosis: How valid a dichotomy for neurons? In: Koliatsos V, Ratan RR, eds. Cell Death and Diseases of the Nervous System. Totowa, New Jersey: Humana Press 1999: 3–28.

54. Galluzzi L, Vitale I, Abrams JM, ***et al.*** Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ 2012; **19**: 107–20.

55. Viallanes H. Recherches sur l'histologie des insectes et sur les phénomènes histologiques qui accompagnent le développement post-embryonnaire de ces animaux. Paris: Masson, 1882.

56. de Bruyne C. Recherches au sujet de l'intervention de la Phagocytose dans le développement des Invertébrés. Arch Biol 1898; **15**: 181–300.

57. Prenant A, Bonin P, Maillard L. Traité d'Histologie, Tome 1. Paris: Schleicher, 1903.

58. Glücksmann A. Cell deaths in normal vertebrate ontogeny. Biol Rev Camb Philos Soc 1951; **26**: 59–86.

59. Lockshin RA, Zakeri Z. Programmed cell death and apoptosis: origins of the theory. Nature Rev Molec Cell Biol 2001; **2**: 545–50.

60. Zakeri Z, Lockshin RA. Cell death: History and future. In: Khosravi-Far R, White E, eds. Programmed Cell Death in Cancer Progression and Therapy. Philadelphia: Springer 2008: 1–11.

61. Kerr JFR. History of the events leading to the formulation of the apoptosis concept. Toxicology 2002; **181**: 471–4.

62. Ндcker G, Vaux DL. A chronology of cell death. Apoptosis 1997; **2**: 247–56.

63. Gupta S. Apoptosis/programmed cell death: A historical perspective. In: Gupta S, Cohen JJ, eds. Mechanisms of Lymphocyte Activation and Immune Regulation VI: Cell Cycle and Programmed Cell Death in the Immune System: v. 6 (Advances in Experimental Medicine and Biology). New York: Plenum Press, 1996.

64. Maghsoudi N, Zakeri Z, Lockshin RA. Programmed cell death and apoptosis — where it came from and where it is going: from Metchnikoff to the control of caspases. Exp Oncol 2012; **34**: 146–52.

65. Weismann A. Die Metamorphose der Corethra Plumicornis. Leipzig: Engelmann 1866.

66. Ganin M. Beiträge zur Erkenntniss der Entwickelungsgeschichte bei den Insecten. Z wiss Zool 1869; **19**: 381–451.

67. Lowne BT. The anatomy and physiology of the blowfly. London: Voorst, 1870.

68. Chun C. Über den Bau, die Entwickelung und Physiologische Bedeutung der Rectaldrüsen bei den Insekten. Abh Senckenb Naturforsch Ges 1876; **10**: 27–52.

69. Helm FE. Über di Spinndrüsen der Lepidopteren. Z wiss Zool 1876; **26**: 434–69.