Cell Death & Differentiation, 4, p.352-361, 1997
Click here to see ERRATUM
Cell Death and Differentiation (1997) 4, 352–361

The growth of the cell death field: an analysis from the ISI-Science Citation Index

Eugene Garfield' and Gerry **Melino**[2,3]

[1] Chairman Emeritus, Institute of Scientific Information, Philadelphia, Pennsylvania, USA
[2] IDI-IRCCS Biochemistry Laboratory and the University of L'Aquila, Italy
[3] corresponding author: IDI-IRCCS Biochemistry Laboratory, c/o Department of Experimental Medicine and Biochemistry, University of Rome Tor Vergata, via Tor Vergata 135, 00133 Rome, Italy tel **t39** 6 20427299; fax t39 6 20427290; email: melino@utovrm.it

It is salutary to reflect that programmed cell ceath (PCD) was first defined as a morphogenetic process over 30 years ago, and apoptosis was defined as a non-inflammatory mechanism for the removal of single cells from complex organs nearly 25 years ago. For many years, these remained essentially descriptive phenomena, and it was not until the recognition of similar processes in C. *elegans*, the identification of those genes regulating nematode apoptosis and the realization that these nematode genes have mammalian homologues, that the field began to expand exponentially. We have asked Andrew Wyllie, John Kerr and Richard Lockshin, some of the pioneers of apoptosis to review the scientific progress of apoptosis. The comments of Richard Lockshin (1997) accompany this paper.

Until recently, apoptosis (ap-öp-tö'sis; from the greek *apo, off + ptosis,* a falling or dropping off) was not listed in major dictionaries. It is now defined as 'a single deletion of scattered cells by fragmentation into membrane-bound particles which are phagocytosed by other cells; believed to be due to programmed cell death' (Stedman's Medical Dictionary, 1995). As PCD/apoptosis emerged as a scientific field in its own right, it became apparent that no existing journal catered specifically to the increasingly varied aspects of the new discipline. *Cell Death and Differentiation* was launched in 1994 to provide a forum dedicated to this topic, accomodating the expansion of the field. In recognition of the linkage between suicidal, proliferative and differentiative decisions, the journal retains 'differentiation' in its title.

The definition, as well as the importance of apoptosis, is evident to the readers of Cell *Death and Differentiation.* Cell death, along with differentiation and growth, is a fundamental aspect of the life cycle of a eukatyotic cell; the control of cell number is the result of the balance between cell loss and gain. The molecular mechanisms leading to the controlled removal of cells in tissues by apoptosis are not fully understood. It is clear that under physiological conditions the process is active, requires energy and the induction/activation of specific genes (Arends *et al,* 1990; Arends and Wyllie, 1991; Schwartz, 1995; Zakeri *et al,* 1995; Peter *et al*, 1996). Genetic studies in the nematode *C. elegans* (Ellis and Hot-vitz, 1986; Ellis *et al,* 1991) have led to the identification of several genes needed for the completion of the cell death program. These genes have been classified into specific functional groups that play distinct roles within the cell death program. The first group of genes includes *permissive* elements which specify which cells will undergo apoptosis. The second group comprises elements whose induction or down-regulation *initiates* the apoptosis pathway. A third set of genes includes *effector* elements required for killing and the subsequent *disposal* and degradation of cellular remnants. Genes with functional homology to some of those defined in C. *elegans* have been described in mammals: Bcl-2 and ted-9, caspases and ted-3. These genes, grown into families of homologous genes, together with additional important regulatory elements, are at the center of intense research efforts to dissect the molecular mechanisms of the death machinery.

Becoming more involved in the dissemination of scientific results, rather than in their creation, inevitably leads to a different perspective on science. The scientific paper is the medium for scientists to communicate their ideas and claims to new knowledge; citations of papers acknowledge the existence of these claims. Therefore, by aggregating citations, bibliometrics aggregates commentaries on early papers providing a means for examining consensus in a field of science. Bibliometric tools can be applied to understand the development of new research fields. The resources at the *Institute for Scientific Information* (ISI) allow for such a detailed analysis of the development of any scientific area by studying the appearance, frequency, citation and co-citation of papers published in that area. In this paper we present the results of a bibliometric study of apoptosis. These data should complement the more traditional historical scientific review by Richard Lockshin (1997, this issue). We invite readers to compare the two approaches for their similarities (and differences).

The primary database used in this study was the ISI-indicators file for 1981 – 1995. In addition, the *Science Citation Index* on CD-ROM and the SCI-Search Dialog file were used as well as ISI's Inventory of Research Fronts.

PCD is a rapidly expanding field

Apoptosis is a field which was identified in 1965 – 1970 through the pioneering work of a long list of eminent scientists. Although cell death was recognized as early as 1899 by Terre (see Lockshin, 1997, this issue of *Cell Death and Differentiation),* this concept remained preliminary and cryptic until the 1960s. For example, the notable paper by Saunders in 1948 (which was cited 459 times before 1992, becoming a 'citation classic', and by now has nearly 550 citations) describes the effect of 'necrosis of the mesodermal cells in the apex of the [chick wing] bud' with 'a rather pronounced contraction or shrinkage of the wing mesoblast'. In fact, the description of this effect of cell death is not fully clear and the author concludes that 'the significance of these results is thus far

rather obscure'. Around 1965, Saunders (1966), Tata (1966) and Lockshin and Williams (1964, 1965a and b) defined the process in insects and the latter author used the term 'Programmed Cell Death' for the first time. In 1972, Kerr, Wyllie and Currie introduced its role in histopathology and cancer with the name 'Apoptosis'. It was not until 1980 that a turning point in the study of apoptosis occurred, when the biochemical methods (DNA fragmentation; Wyllie *et al*, 1980a, b) which supported its morphological characteristics were identified (Bowen and Lockshin, 1981). Later, in the mid 1980s, Horvitz (Sulston and Horvitz, 1977; Horvitz *et al*, 1983; Ellis and Horvitz, 1986; Ellis *et al*, 1991; Hengartner *et al*, 1992) outlined a series of genes related to PCD in C. *elegans*. Around 1991 the molecular mechanism begun to be understood with the identification of the role of CD95 (APO-1/Fas) (Trauth *et al*, 1989; Itoh *et al*, 1991), Bcl-2 (Sentman et *al*, 1991), p53 (Yonish-Rouach et *al*, 1991), and c-myc (Evan *et al*, 1992). After 1991, the field had evidently become widely recognized. Consequently, the number of papers published increased to the present level of 5,000 per year.

Between 1980– 1996 at least 20,000 papers were published on cell death. It compares in size to other new fields, such as nitric oxide (NO), with 30,000 papers, and p53, with 17,500 papers. However, while these two other fields developed rapidly immediately after their identification, PCD started in 1960 with a long lag phase of only about 100 papers per year; then, from 1991 onward, the number of papers published each year exploded.

Figure 1 shows the annual output of papers published on apoptosis since 1970.

Increasing impact of PCD papers

The exponential growth in the number of papers published since 1990 has been accompanied by an increase in citation impact. In fact, the average number of citations per paper rose from four to 14. Figure 2 shows the pattern of mean citation-per-paper distribution over 5-year windows. The 5,900 papers published between 1981 – 1996 on cell death/apoptosis (listed in the title) received 80,000 citations, with a mean of 13.5 citations per paper. Two observations are noteworthy: first, average citations have risen from circa 3.5 -4 to over 13.5 over the last decade, showing a significant increase in impact; and second, there is a certain level of uncitedness. The 13.5 mean citations arises from the group of highly cited papers. Of these 5,927 published papers, 2,870 were never cited, 538 were cited only once and 290 were cited twice. That is, over 62% of published papers received less than two citations.

PCD is now one of the hottest areas of science. In fact, among the 10 most-cited scientific papers published in 1995 and cited in 1995, four concern PCD: (4th) Dhein J et *al* (1995), (55 cites); (5th) Brunner T *et al* (1995) (49 cites); (6th) Ju ST *et al* (1995) (47 cites); (10th) Miyashita T and Reed JC (1995) (38 cites).

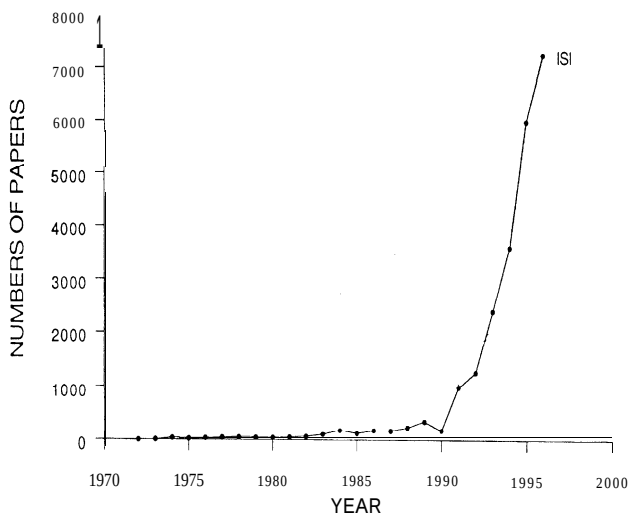

Figure 1 Trend of increasing number of papers on PCD from 1970 until 1996

Late recognition effect

The citation analysis literature provides only a few documented examples of delayed recognition. In the early 70s the classic paper by Kerr *et al* (1972) was cited in less than 20 papers per year. Twenty years later, by 1991, it had been cited in more than 400 publications. In 1995 alone it was cited over 400 times. Figure 3 shows the number of citations recorded for some early relevant papers published on PCD. The paper by Kerr *et* al, 1972 (bold line) shows the strongest 'delayed recognition effect'.

Figure 3 shows two different trends. While other papers on human pathology and cancer show the same effect to a lesser degree, the early papers on insect models did not show this delayed recognition effect. This might be due to the smaller scientific community studying these models.

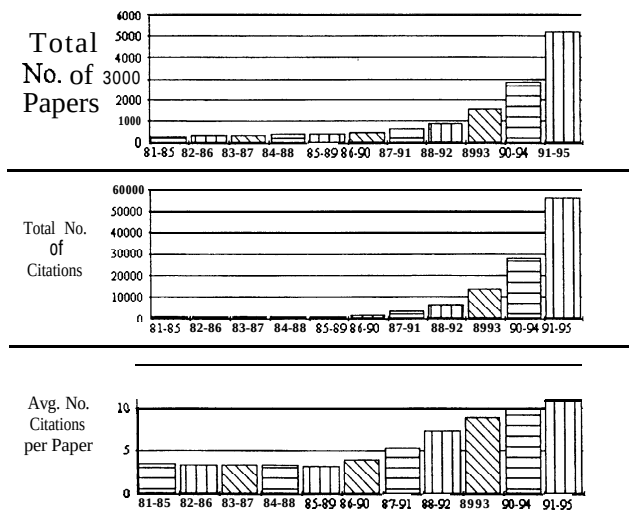

Figure 2 Trend of increasing mean citation per paper. From a restricted 5927-paper database, the top panel shows the number of papers published every 5 years, the middle panel shows the total number of citations, and the lower panel the average number of citation per paper. The increase in number of papers published is parallel to the increase in impact, evaluated as citations

Areas of interests and country origins of papers

The major areas in which PCD papers are published are cancer, immunology, AIDS, embryology, development, pathology, pharmacology and toxicology. These data are reported in Figure 4.

In order to evaluate certain differences in the field, we have divided the papers published into ear/y *period (1972-* 1987; 1 , *146* papers) and *late period* (1995 – 1996; 9,722 papers) papers. The *middle period* (1988- 1994) shows an intermediate pattern (data not shown).

As shown in Figure *5,* both early and late papers came predominantly from Europe and North America, although Australia was significant in the early years. Today relatively few papers come from the rest of the world.

Distribution of papers in different journals

Table 1 ranks the journals publishing papers on PCD by frequency. The data have been divided into *ear/y* (panel A, 1972 – 1987; 1 ,146) and *late* (panel B, 1995- 1996; 9,722) papers. No one journal collects more than 3% of the papers.

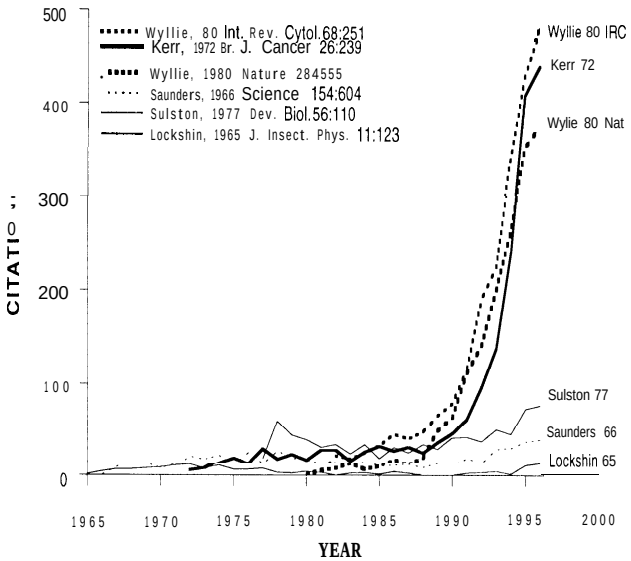

Figure 3 Late recognition effect of some early papers on Cell Death. The paper by Kerr et *al*. 1992 shows the most striking delayed recognition effect

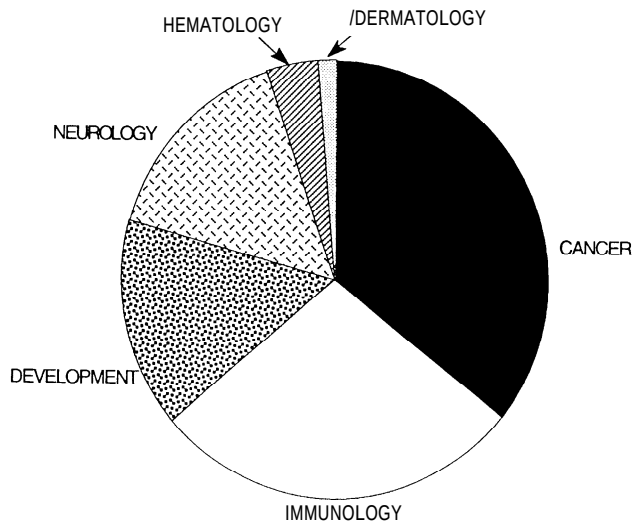

Figure 4 Areas of interest. The papers published in the period 1981 – 1995 were classified by area of interest. Some papers have been assigned to more than one field

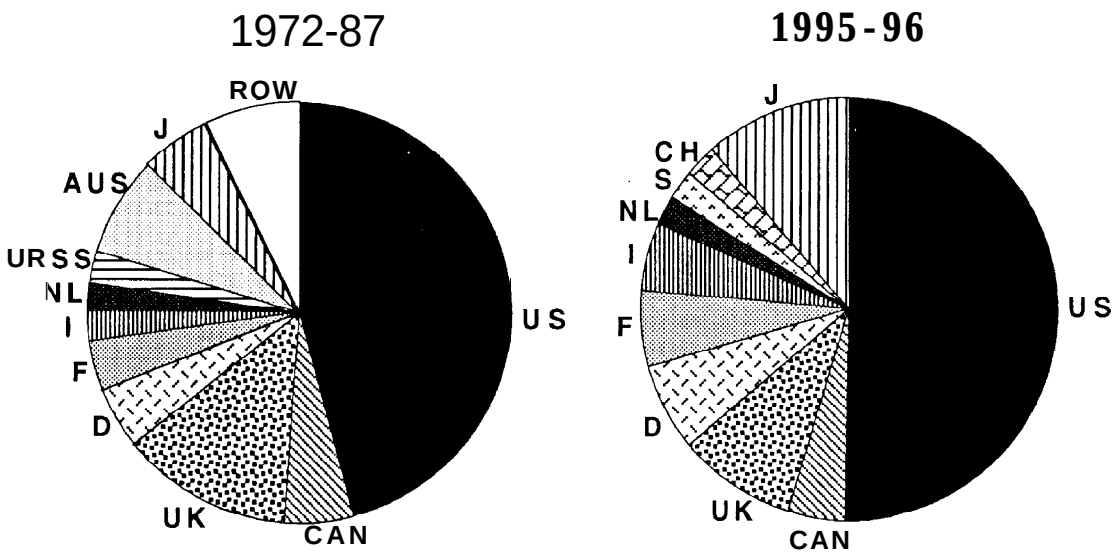

Figure 5 Country of origin of papers published on PCD. (left panel) Papers published between 1972- 1987; total count 1,100. (right panel) Papers published between 1995 1996; total count 9,700. Legend: ROW, Rest of World; J, Japan; AUS, Australia, URSS, Russia; NL, Netherlands I, Italy; F, France; D, Germany; UK, United Kingdom; CAN, Canada; US, United States; CH, Switzerland, S, Sweden

Only recently have new journals dedicated mainly to PCD emerged: Cell Death and *Differentiation* was launched in late 1994, and *Apoptosis* in late 1996. Although it is relatively new, Cell Death and *Differentiation* already ranks 16th in output in the SCI category of 103 Cell Biology journals. Its impact factor in 1995 was 4.250.

Early (1972- 1987) PCD papers were published predominantly in pathology or anatomical journals with lower impact factors. Late (1995- 1996) papers appeared in basic science and immunology journals.

More recently, PCD papers have begun to appear in clinical journals. Publications have shifted from pathology studies into basic research, followed by pharmacological and clinical studies, thereby reflecting the maturation of the field.

The most cited

Even though the classic papers published before 1980 were well known to those familiar with PCD, Table 2 demonstrates how citation analysis confirms the primordial role of these papers.

Tables 3 and 4 show the most cited, authors, and organizations published/publishing for 1981 – 1995. The data were compiled from 5,927 papers (1981 – 1995) in which 'apoptosis' and/or 'cell-death' appeared in the title. Table 5 shows the most cited apoptosis papers published and cited in 1996.

Table 1 Journals publishing papers on Apoptosis or Cell Death

(A) year 1972:1987 total=1 146 items			(B) year 1995:1996 total=9722 items		
Rank	Papers	Journal	Rank	Papers	Journal
1	34	Anatomical Record	1	310	Journal of Immunology
2	29	Journal of Comparative Neurology	2	301	Blood
3	23	Cancer Research	3	251	FASEB Journal
4	22	Journal of Pathology	4	189	Cancer Research
5	21	American Journal of Pathology	5	184	Journal of Biological Chemistry
6	20	Developmental Biology	6	184	Proceed the Nat Acad Science
7	19	Journal of Neuroscience	7	141	Oncogene
8	19	Teratology	8	140	Gastroenterology
9	18	Internat Jour Radiation Biology	9	137	Journal of Experimental Medicine
10	18	Radiation Research	10	116	Biochem Biophys Res Comm
11	17	Developmental Brain Research	11	114	European Journal of Immunology
12	17	Federation Proceedings	12	108	Investig Ophthalm & Visual Science
13	16	Anatomy and Embryology	13	89	British Journal of Haematology
14	15	Journal of Cell Biology	14	88	Journal of Neurochemistry
15	14	Journ Embryol Experiment Morphol	15	87	Journal of Virology
16	14	Proceed Nation Academy Science	16	86	Cell Death and Differentiation
17	13	Brain Research	17	83	American Journal of Pathology
18	12	Journal of Immunology	18	80	Journal of Cellular Biochemistry
19	12	Nature	19	77	Journal of Investigative Dermatology
20	11	British Journal of Cancer	20	76	Cellular Immunology
21	11	Cell and Tissue Research	21	75	Journal of Neuroscience
22	11	Experimental Neurology	22	74	Experimental Cell Research
23	11	Journal of Anatomy	23	69	Nature
24	11	Journal of Investigative Dermatology	24	68	Laboratory Investigation
25	11	Tsitologiya	25	67	Brain Research
26	IO	Clinical Research	26	66	EMBO Journal
27	IO	Journal of Radiation Research	27	63	FEBS Letters
28	9	Cell and Tissue Kinetics	28	61	International Journal of Cancer
29	9	Proceed Americ Association Can	29	61	Molecular Biology of the Cell
30	8	Science	30	60	Molecular and Cellular Biology
31	7	American Journal of Anatomy	31	59	Journal of Clinical Investigation
32	7	Journal of Dental Research	32	59	Science
33	7	Laboratory Investigation	33	58	International Immunology
34	7	Mutation Research	34	58	Leukemia
35	7	Neuropathol Applied Neurobiology	35	57	Experimental Hematology
36	6	Acta Anatomica	36	56	Hepatology
37	6	Circulation	37	56	Neuroscience Letters
38	6	Experimental Cell Research	38	54	Cell Growth & Differentiation
39	6	Hepatology	39	53	British Journal of Cancer
40	6	Journal of Experimental Zoology	40	52	International Journal of Oncology
41	6	Phytopathology	41	52	Jour Am Soc Nephrology
42	5	Biochem Biophys Research Communic	42	46	Circulation
43	5	Bullet Experiment Biology Medicine	43	45	Cell
44	5	Endocrinology	44	44	Immunology
45	5	Histochemical Journal	45	42	Immunity
46	5	International Review of Cytology	46	40	Neuroreport
47	5	Japanese Circulation Journal-Engl Edit	47	40	Neuroscience
48	5	Journal of Cell Science	48	39	Anticancer Research
49	5	Journal of Physiologiogy-London	49	39	Clinical Cancer Research
50	5	Journal of Theoretical Biology	50	39	Journal of Comparative Neurology

Sub-development: research fronts, SCI-Maps and cluster strings

Co-citation analysis involves the application of clustering and scaling methods to data on the number of times earlier papers are cited together by later papers. The building of nested sets of clusters allows us to view science with various degrees of resolution, from narrowly focused problem areas to entire disciplines, from cross-sectional representations to longitudinal changes in order to obtain patterns of continuity. For several decades, ISI has identified Research Fronts using the method of co-citation analysis (Small, 1994; Small and

Table 2 Most cited papers on apoptosis/cell death

			Citations		Rank*		
Rank	Paper's first author and source		Real	Expected	CD*	A*	Country
*(A) Papers published in 1960- 1980***							
1.	Wyllie	Int Rev Cytol (1980) 68: 251	1908				
2.	Kerr	Br J Cancer (1972) 26: 239	1624				
3.	Wyllie	Nature (1980) 284: 555	1428				
4.	Sulston	Dev Biol (1977) 56: 110	762				
5.	Saunders	Science (1966) 154: 604	508				
(B) Papers published in 1981 1993							
1.	Hockenbery	Nature (1990) 348: 334	875	95.72	1		US
2.	Cohen	J Immunol (1984) 132: 38	817	47.97	2		US
3.	Vaux	Nature (1988) 335: 440	740				
4.	Smith	Nature (1989) 337: 181	737	97.39		1	UK
5.	Evan	Cell (1992) 69: 119	719	115.12		2	UK
6.	YonishRouach	Nature (1991) 352: 345	712	82.08		3	F
7.	Wyllie	J Pathology (1984) 142: 67	636	23.4		4	UK
8.	Lowe	Nature (1993) 362: 847	635	48.05		5	UK
9.	Clarke	Nature (1993) 362: 849	609	48.05		6	
10.	Itoh	Cell (1991) 66: 233	594	144.98		7	J
11.	Arends	Am J Pathol (1990) 136: 593	557	27.06		8	UK
12.	Oppenheim	Ann Rev Neur (1991) 14: 453	539	150.80	3		us
13.	Raff	Nature (1992) 356: 397	539	148.64	4		UK
14.	Gavrieli	J Cell Biol (1992) 119: 493	526	37.13	5		us
15.	Sulston	Dev Biol (1983) 100: 64	521				
16.	WatanabeFu	Nature (1992) 356: 314	515	65.29		9	J
17.	Williams	Nature (1990) 343: 76	512	95.72		10	UK
18.	Farber	Life Sci (1981) 29: 1289	484	111.64	6		us
19.	Trauth	Science (1989) 245: 301	461	113.54		11	D
20.	Hockenbery	Cell (1993) 75: 241	435	80.23		12	us
21.	Sentman	Cell (1991) 67: 879	428	144.98		13	
22.	Ellis	Ann Rev Cell Biol (1991) 7: 663	398	108.74	7		
23.	Hockenbery	PNAS (1991) 88: 5961	378	45.60	8		us
24.	Henderson	Cell (1991) 65: 1107	366	144.98	9		
25.	Oltavi	Cell (1993) 74: 609	348	80.23	10		us
26.	Shaw	PNAS (1992) 89: 4495	346	32.43		14	
27.	Boise	Cell (1993) 74: 597	338	80.23	11		us
28.	Groux	J Exp Med (1992) 175, 331	325	44.74		15	
29.	Lemasters	Nature (1987) 325: 78	325	111.70	12		
30.	Kawabe	Nature (1991) 349: 245	323	82.08	13		
31.	Bissonnette	Nature (1992) 359: 552	321	65.29	14		us
32.	Cohen	Ann Rev Immunol (1992) 10: 267	320	107.30	15	16	us
33.	Nicoletti	J Immunol Meth (1991) 139: 271	318	8.86		17	I
(C) *Papers published in 1994*							
1.	Eldeiry	Cancer Res (1994) 54: 1169	227	12.83			
2.	Reed	J Cell Biol (1994) 124: 1	199	21.58			
3.	Shi	Science (1994) 263: 1143	131	19.56			
4.	Buttke	Immunol Today (1994) 15: 7	112	11.33			
5.	Vaux	Cell (1994) 76: 777	111	50.28			
6.	Wang	Cell (1994) 78: 739	98	37.32			
7.	Yin	Nature (1994) 369: 321	98	24.48			
(D) Papers published in 1995							
1.	Brunner	Nature (1995) 373: 441	59	4.06			
2.	Ju	Nature (1995) 373: 444	55	4.06			
3.	Thompson	Science (1995) 267: 1456	40	9.54			
4.	Roy	Cell (1995) 80: 167	32	6.70			
5.	Boudreau	Science (1995) 267: 891	29	3.37			
6.	Yang	Cell (1995) 80: 285	29	6.7			
7.	Alderson	J Exo Med (1995) 181: 71	28	1.75			

Citations were counted up to October 1996 from the SCI database on Cell-Death and Apoptosis (1980 1995; 5,927 items). *=Ran using as title's keyword Cell-Death (CD) or apoptosis (A). **-Citations were retrieved from the main SCI database; since these items are too old, before the existing SCI database, the papers were selected on an empirical anecdotal base, without the use of algorithms.

Greenlee, 1995). The algorithm clusters papers on the basis of variable thresholds of co-citation, thereby grouping papers that are frequently cited together by other authors. From the 600,000 papers published each year, about 10,000 Research Fronts will be identified. Each of these will consist of two to 50 core cited papers as well as the variable number of citing papers each year. The average annual cluster will contain about 40 citing (current) papers. It is a purely computational procedure based on citation links and is, in fact, a means of automatic classification. Clusters vary from a small group of papers up to thousands defining a discipline.

The first SCI Research Front on PCD identified emerged in 1984, several years after the initial papers were published. This research front consisted of three co-sited core documents, each of which was cited separately, as shown:

1. Saunders JW Science (1966) 154: 604-612 frequency 17
2. Kerr JFR ef al Brit J Cancer (1972) 26: 239-257 frequency 27
3. Wyllie AH et al Int Rev Cytol (1980) 68: 251 -306 frequency 29

In the following years, PCD continued to appear on only one research front. The subsequent proliferation of PCD research can be seen in the increased number of clusters and the number of core documents (data not shown). In 1991 – 1992, the field expanded dramatically and began a process of 'twigging', or the splitting off and proliferation of research areas that develop in parallel. This indicates the growth and the progression of PCD research through the cluster-level hierarchy. In fact, by 1994, the number of Research Fronts had expanded to 17 (Figure 6), indicating the ongoing evolution of PCD as a research field.

Figure 6 reports the Research Fronts identified until 1992 and 1994 (the last years to be evaluated since the analysis was performed in alternate years this decade). The cluster strings show an interesting pattern, corresponding either to models (prostate, thymus, nervous system), or molecules (Bcl-2, CD95). It is evident that the area of PCD is subdividing into divergent fields. The character of the research has also changed from descriptive morphological studies to the analysis of the molecular mechanisms involved, and it is becoming clear that the clinical implications are opening therapeutic applications (Knight, 1995; Gougeon, 1995; Ameisen et al, 1995; Wyllie, 1996; Krammer, 1996, 1997).

In order to evaluate the relationship between different research sub-areas, cluster maps can be created using multidimensional scaling. This algorithm uses a measure of association among objects as input, normalized co-citation links, producing a spatial representation of those objects in

Table 3 Most cited authors on apoptosis/cell death (1981 – 1995)

Rank	Author	Cites	Papers	Avg.Cites/Paper
1.	Wyllie AH	4190	41	102.20
2.	Korsmeyer SJ	3292	30	109.73
3.	Williams GT	2242	20	112.10
4.	Cohen JJ	2129	25	85.16
5.	Oppenheim RW	1671	27	61.89
6.	Green DR	1604	41	39.12
7.	Nunez G	1495	26	57.50
8.	Nagata S	1402	15	93.47
9.	Cotter TG	1328	32	41.50
10.	Horvitz HR	1298	13	99.85
11.	Raff MC	1251	11	113.73
12.	Jacks T	1203	11	109.36
13.	Yuan JY	1172	13	90.15
14.	Lotem J	1115	11	101.36
15.	Sachs L	1115	12	92.92
16.	Isaacs J	1089	21	51.86
17.	Reed JC	1063	31	34.29
18.	Osborne BA	975	14	69.64
19.	Oren M	944	12	78.67
20.	Martin SJ	923	28	32.96
21.	Evan GI	915	13	70.38
22.	Krammer PH	914	28	32.64
23.	Kyprianou N	894	13	68.77
24.	Schultehermann R	884	23	38.43
25.	Haslett C	872	28	31.14
26.	Yonehara S	871	13	67.00
27.	Bursh W	866	25	34.64
28.	Lemaster JJ	853	20	42.65
29.	Dive C	852	20	42.60
30.	Orrenius S	839	43	19.51
31.	Eastman A	830	19	43.68

Citations were counted up to October 1996 from the SCI database on Cell-Death and Apoptosis (1980- 1995; 5,927 items). Only authors with more than 10 papers were included.

Table 4 Most cited organizations on apoptosis/cell death (1981 – 1995)

Rank	Author	Cites	Papers	Avg. Cites/ Paper
1.	Washington Univ, St. Louis	4785	81	59.07
2.	Univ Edinburgh	4529	62	73.05
3.	Univ Birmingham	3488	56	62.29
4.	Univ Colorado	3047	84	36.27
5.	MIT	2990	38	78.68
6.	Univ N Carolina	1841	73	25.22
7.	NCI	1727	83	20.81
8.	Johns Hopkins Univ	1578	97	16.27
9.	Univ Massachussetts	1451	40	36.28
10.	Inst Pasteur	1447	64	22.61
11.	Osaka Biosci Inst	1402	14	100.14
12.	Wake Forest Univ	1391	27	51.52
13.	Weizmann Inst Sci	1364	36	37.89
14.	Univ London Univ Coll	1343	23	58.39
15.	La Jolla Inst Allergy & Immun	1329	45	29.53
16.	St Patricks Coll	1327	26	51.04
17.	Harvard Univ	1306	114	11.46
18.	Univ Queensland	1227	67	18.31
19.	Karolinska Inst	1225	71	17.25
20.	Imperial Canc Res Fund	1184	31	38.19
21.	La Jolla Canc Res Fund	1155	33	35.00
22.	Stanford Univ	1126	69	16.32
23.	Univ Texas	1118	160	6.99
24.	Univ Vienna	1040	30	34.67
25.	Hammersmith Hosp	998	42	23.76
26.	Univ Heidelberg	958	30	31.93
27.	Natl Jewish Ctr Immunol	951	16	59.44
28.	Christie Hosp & Holt Rad In	950	22	43.18
29.	Univ Manchester	905	43	21.05
30.	German Cancer Res Ctr	884	31	28.52
31.	Univ Alberta	878	16	54.88

Citations were counted up to October 1996 from the SCI database on Cell-Death and Apoptosis 1995; 5,927 items).

Table 5 Hottest research on apoptosis/cell death in 1996

A. Hot research papers of 1996

Rank	Paper	Citations
9.	Hsu, H *et al*, TRADD-TRAF2 and TRADD-FADD interactions define two distinct TNF receptor 1 signal transduction pathways. Cell 84(2): 299–308 (26 January 1996)	44
11.	Duan, H *et al*. ICE-LAP3, a novel mammalian homologue of the C. elegans cell death protein Ced-3 is activated during Fas- and TNF-induced apoptosis J. Biol. Chem. 271(3): 1621–1625 (19 January 1996)	40
13.	Graeber, TG *et al*. Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours Nature 379(6560): 88–91 (4 January 1996)	39
17.	Verheij, M *et al*. Requirement of ceramide-initiated SAPK/JNK signalling in stress-induced apotosis Nature 380(6569): 75–79 (7 March 1996)	35
23.	Chinnaiyan, AM *et al*. Molecular ordering in the cell death pathway J. Biol. Chem. 271(9): 4573–4576 (1 March 1996)	29
37.	Enari, M *et al*. Sequential activation of ICE-like and CPP32-like proteases during Fas-mediated apoptosis Nature 380(6576): 723–726 (25 April 1996)	25

B. Scientists ranked by number of Hot Papers in 1996

Rank	Name and institution	Hot Papers
2.	Vishva M. Dixit, University of Michigan	7
8.	Douglas R. Green, La Jolla Inst. Allergy & Immunol.	5

Citations and ranking were obtained from ISI's Hot Papers Database. For more details see: Anonymous (1997) 'The Hottest Research of 1996' Science Watch 8:1,2

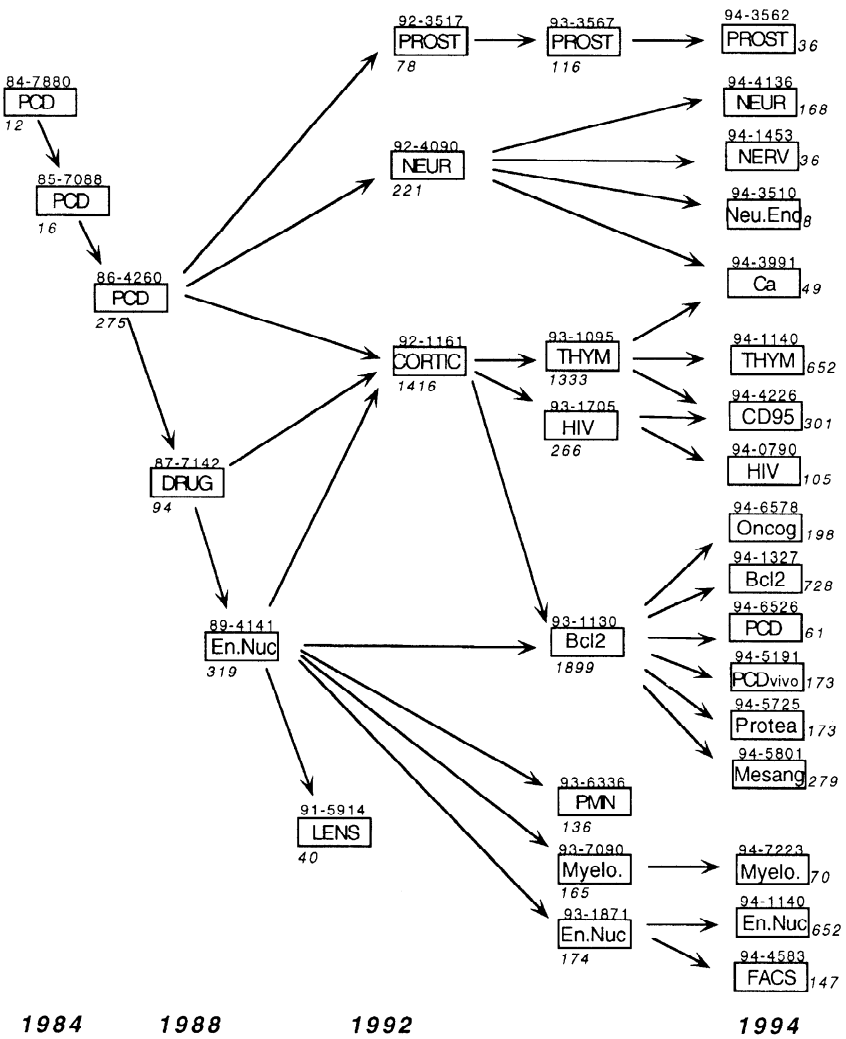

Figure 6 Research Fronts on Cell Death/Apoptosis. An abbreviated Research Front name is shown inside the box. The serial number on the top includes the year of Research Front. The number below shows the number of papers published that year on that Research Front topic

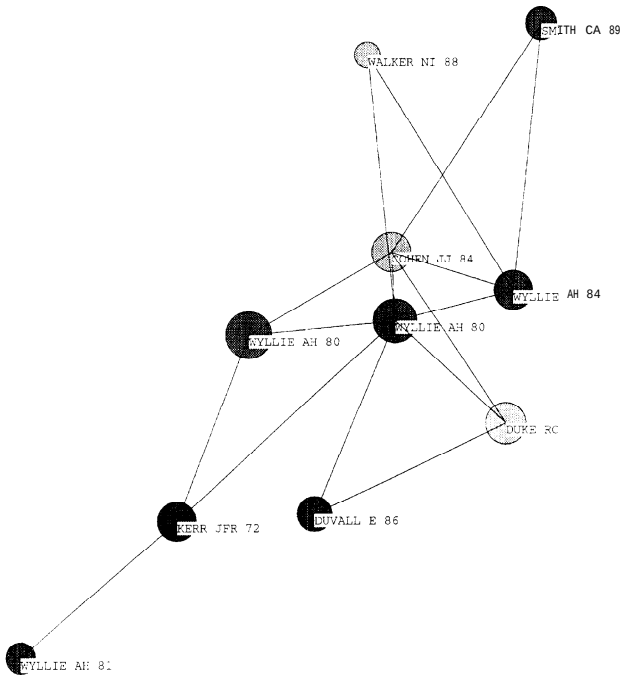

Figure 7 SCI-Map using as a seed paper Wyllie et al. 1980. Other papers were added based on co-citations, see text for details. These papers were part of the 1984 and subsequent Research Fronts (see text and Figure 6)

a specified number of dimensions (two in this case) but multidimensional in the case of experimental prototype maps. These representations are referred to as 'maps of science' since they describe the relationship between papers, fields or areas, and therefore between scientific ideas. SCI-Map is a ISI PC program running under Microsoft Windows; it takes input data on nodes and links, creating clusters node by node on screen, forming a network. In this case, nodes are papers, and links must have numerical similarity values ranging from zero to one, the inter-node distances are computed by a logarithmic transformation of the similarity values. The document is base on geometric triangulation (rather than other more mathematically based mapping methods) of the strongest interdocument links, in an attempt to represent intrinsic associations among items. We select a starting document or 'seed' node and then add nodes one by one (according to qualifying, ordering and inclusion rules) which are displayed on the screen with their links as they are added. The seed paper affects the geometry of the cluster formed and the order in which nodes are added, similarly to the chaos theory.

Figure 7 is a 'SCI-Map' showing the co-citation relationship of several early papers on PCD. This is a lower-level map with only a few papers to show the early aggregations to the seed paper. The SCI-Map started with a seed paper (Wyllie et al, 1980b) from which the computer algorithm identified the closest papers in term of co-citations. Each circle represents one paper and the length of the connecting string is proportional to co-citations found in the papers, indicating the 'similarity' of the papers. Interestingly, the results show (i) another paper (Kerr et al, 1972) with which it co-defines the Research Fronts in 1984, 1985, 1986, 1987, 1989; (ii) two papers (Wyllie et al, 1980a; Cohen and Duke, 1984) from the 1986 and 1989 Research Front; (iii) three papers (Duke, 1983; Duvall, 1986; Smith et al, 1989) from the 1989 Research Front. These close connections show how strongly related the papers forming the early Research Fronts are; these papers led to the first clear identification of the field.

Finances

The increased interest in cell death has affected the research funding system both at public and private levels. In fact, the National Institutes of Health funding of extramural grants on cell death has more than doubled each year since 1992, when 78 projects were funded with 12 million dollars (Lewis, 1995). A similar trend has been observed for the European Union. Similarly, pharmaceutical and biotechnology industries have invested more and more resources for studies on cell death.

In the last 3 -4 years, several new start-up biotechnology companies have been formed whose principal scientific and commercial activities are aimed at PCD: Apoptosis Technology Inc. (Cambridge, MA); IDUN Pharmaceuticals (San Diego, CA); LXR Biotechnology (Richmond, CA); *ONYZ* Pharmaceuticals (Richmond, CA).

Other companies with wider interests also have research groups on PCD: Bristol-Myers Squibb (Wallingford, CT); Ciba-Geigy (Basel, Switzerland & Summit, NJ); Genentech (South San Francisco, CA); Glaxo (Geneva & London); Hoechst-Roussel Pharmaceutical (Sommerville, NJ); Hoffmann-La Roche (Nutley, NJ); L'Oreal (Paris, France); Marion Merrel Dow (Cincinnati, OH); Merck (Rahway, NJ) and Merck-FROSST (Point Claire, Quebec, Canada); Oncor (Gaithersburg, MD); Pfizer (Groton, CT); Sandoz Pharmaceuticals (East Hannover, NJ); Schering-Plough (Dardilly, France); Wellcome Research Laboratories (Beckenham, Kent UK).

In addition to these companies, others have also developed interests directed at apoptosis.

Antisense therapy: Lynx Therapeutics (Hayward, CA); CV Therapeutics (Palo Alto, CA); Genetic Therapy (Gaithersburg, MD); etc.

Gene therapy: Alkermes (Cambridge, MA); Canji (San Diego, CA); GeneMedicine (Houston, TX); Genetic Therapy (Gaithersburg, MD); Megabios (Burlingame, CA); Myriad Genetics Salt Lake City, UT); Sennes Drug Innovations (Houston, TX); Synergen (Boulder, CO); etc.

Calpain Inhibitors: Cortex Pharmaceuticals (Irvine, CA); Alkermes (Cambridge, MA); etc.

ICE *Inhibitors:* (Seattle, WA), Vertex Pharmaceuticals (Cambridge, MA), Sterling Winthrop (Collegeville, PA), etc.

NMDA Inhibitors: Cambridge Neuroscience (Cambridge, MA); Guildford Pharmaceuticals (Baltimore, MD); Symphony Pharmaceuticals (Malvern, PA); Synthelabo (Paris, France); etc.

NO Inhibitors: NitroMed (Cambridge, MA); Monsanto (St. Louis, MO); Guildford Pharmaceuticals (Baltimore, MD); etc.

Neurotrophic factors: Cephalon (West Chester, PA); American Cyanamid (Wayne, NJ); Kaken Pharmaceuticals (Tokyo, Japan); etc.

Receptor modulators: Receptagen (Edmonds, WA); Ligand Pharmaceuticals (San Diego, CA); etc.

However, because of the extremely rapid evolution of the field, vast scientific areas have not yet been commercially explored. PCD therefore offers good possibilities for biotechnology. A more updated and precise analysis of this rapidly changing situation is far beyond the scope of this paper.

A terminology problem

The restricting point in an evaluation of this sort is the use of correct terminology. In fact, the field was slowly recognized over a period of 20 years by different scientists working in different fields who did not always use the same terminology. The term 'Programmed Cell Death' first identified by Richard A. Lockshin in 1964 has been used in the US, while 'Apoptosis' introduced by Andrew H. Wyllie in 1972 was preferred in Europe. Other scientists are more general in their use of the term 'Cell Death'. Several attempts have been made to define the scientific differences between these three terms, but this goes beyond the scope of our analysis and is possibly academic since the vast majority of authors use either term interchangeably.

The results of the analysis depend on the correct choice of a keyword. For example, the analysis published in *The Scientist* (Lewis, 1995) reported a list of the most-cited papers in the field:

1. Smith CA *et a/,* 1989 539 cites (1981- 1994) UK
2. Wyllie AH *et al,* 1984 450 cites (1981 – 1994) UK
3. Yonish-Rouach E *et al,* 1991 357 cites (1981- 1994) France
4. Williams GT *et al,* 1990 340 cites (1981 – 1994) UK
5. Arends MJ *et al,* 1990 294 cites (1981- 1994) UK
6. Evan GI *et al,* 1992 288 cites (1981- 1994) UK
7. Itoh N *et al,* 1991 271 cites (1981 – 1994) Japan
8. Sentman CL *et al,* 1991 229 cites (1981- 1994) US
9. Trauth BC *et al,* 1989 217 cites (1981 – 1994) Germany
10. Murphy KM *et al,* 1990 188 cites (1981- 1994) US

Searching for 'apoptosis' skews the results towards (i) European authors, and (ii) immunologists. In fact, neurologists and embryologists tend to favor the term 'programmed cell death'. Similarly, using 'apoptosis' alone as a title-keyword search in the SCI- database, the authors of the above analysis (Lewis, 1995) found that eight out of ten top papers were authored by Europeans. This does not mean that most of the important science has been done in Europe, but merely that Europeans used the word 'apoptosis' more often in the titles of their papers. Other highly respected scientists were not included, simply because they used the term 'cell death' in their papers, and were thus not retrieved. In fact Table 2B shows the rank each paper would have had searching only with the title's keyword Cell-Death (Rank-CD*) or Apoptosis (Rank-A*). The two lists are clearly different, as US authors tended to use the word Cell-Death rather than apoptosis, at least during the earlier years.

To correct that situation we used both terms in the analysis in Table 2, showing the ranking of the most cited papers in 1960- 1980 (Table 2A), in 1981- 1993 (Table 2B), in 1994 (Table 2C), and in 1995 (Table 2D).

Most analyses performed in this report used the term 'Apopt(free ending)' and/or '(free) Cell (free ending) Death', unless otherwise stated. These terms were searched in the title and keywords, unless otherwise stated.

A cautionary tale

We report the bibliometric evaluation of the field of cell death over the last 3 decades, with the more recent pattern of subdivision. Our data demonstrate the use of the *Science Citation Index* in evaluating various facets of a scientific topic. The same methodology can be applied to any area of science to elucidate development and other patterns of interest to scientists, publishers and historians. What is the significance of the merging and splitting patterns in the course of development of PCD research? Can cluster proximity on higher-level maps forecast a merger and synthesis of areas later on? Can maps be used to suggest hypotheses that scientists could fruitfully explore at the experimental level? Will a breakthrough come from within the field itself or from some seemingly unrelated or fringe territory of research? As described by Small (1994) bibliometrics never claimed to offer insights into scientific knowledge, but the tools of bibliometrics can in fact be put at the service of advancing scientific knowledge in actual practice.

The complexity of the growth of PCD may be highlighted not only by the presence of multiple highly complex molecular mechanisms (transcription factors, effectors, receptors, binding proteins, degrading enzymes), but also by the concomitant presence of methodological progress (morphology, DNA ladder) and models (insects, cancer, C. thymus, prostate). The result of all this work will increase the understanding of the field.

Cell death by apoptosis is currently thought to consist of several convergent step-by-step regulated processes which are reversible until a late common execution stage. In fact, it is now clear that many agents are able to induce apoptosis in different cell types and under various physiological or experimental circumstances. Thus, it is reasonable to expect that the expression of the putative apoptotic genes should be controlled by multifunctional promoters; future studies will certainly lead to the identification of unknown regulatory steps which are very likely related to new biological functions and which may represent target points for the control of the death program with obvious therapeutic implications. In conclusion, although many aspects of the biology of PCD remain speculative, clarification of the mechanisms by which different factors control cell surival and cell death will lead to the understanding of many diseases that affect growth

and degeneration. Early clinical studies seem to promise new pharmaceutical developments.

Martin Raff (1996) brings the serious philosophical problem hunted by Albert Camus and Jean Paul Sartre, that is suicide ... to a microscopic scale. To what extent is ceil suicide an individual decision and to what degree a social one? To what extent is ceil death balancing ceil growth? is necrosis 'dead'? When talking of ceil death, we have to be careful not to lurch from one fashionable extreme to the other. Perhaps because of the frequency and therapeutic intractability of human cancer, more emphasis has been laid on cell proliferation and its control than on ceil death and differentiation. Now, it seems? the perspective favours death, and pathological proliferation is regarded as inappropriate evasion of physiological death. A growth factor is now an anti-death factor. Death is the default option for the ceil. And so on and so on. Perhaps, indeed, we have subconsciously excluded 'proliferation' from the title of Cell *Death and Differentiation* for these reasons, too.

Acknowledgements

The authors would like to thank Henry Small and Barbara Temos of ISI, Sharon Murphy of The Scientist and Sarah Sherwood of Cell Death and Differentiation for their valuable technical support.

References

Ameisen JC, Estaquier J, Idziorek T and De Beis F (1995) Programmed cell death and AIDS: significance, perspectives and unanswered questions. Cell Death Differ. 2: 9-22

Arends MJ and Wyllie AH (1991) Apoptosis. Mechanism and role in pathology. Int. Rev. Exp. Pathol. 32: 223-254

Arends MJ, Morris RG and Wyllie AH (1990) Apoptosis- The role of the endonuclease. American Journal of Pathology 136: 593 – 608

Bowen ID and Lockshin RA eds. (1981) Cell Death in Biology and Pathology. Chapman and Hall, London

Brunner T, Mogil RJ, Laface D, Yoo NJ, Mahboubi A, Echeverri F, Martin SJ, Force WR, Lynch DH, Ware CF and Green DR (1995) Cell-autonomous Fas (CD95)/Fas-ligand interaction mediates activation- induced apoptosis in T-cell hybridomas. Nature 373: 441- 444

Cohen JJ and Duke RC (1984) Glucocorticoid activation of a calcium-dependent endonuclease in thymocyte nuclei leads to cell death. J Immunol. 132: 38 – 42

Dhein J, Walczak H, Baumler C, Debatin K-M and Krammer PH (1995) Autocrine T-cell suicide mediated by APO- 1 /(Fas/CD95) Nature 373: 438 – 441

Duke RC (1983) Endogenous endonuclease-induced DNA fragmentation: an early event in cell mediated cytolysis. PNAS 80: 6361 -6365

Duvall E and Wyllie AH (1986) Death and the cell. Immunol Today 7: 115

Ellis H and Hotvitz H (1986) Genetic control of programmed cell death in the nematode C. elegans. Cell **44: 817-829**

Ellis RE, Yuan J and Horvitz HR (1991) Mechanism and functions of cell death. Annu. Rev. Cell Biol. 7: 663-698

Evan GI, Wyllie AH, Gilbert CS, Littlewood TD, Land H, Brooks M, Waters CM, Penn LZ and Hancock DC (1992) Induction of apoptosis in fibroblasts by c-myc protein, Cell69: 119-128

Gougeon ML (1995) Does apoptosis contribute to CD4 T cell depletion in human immunodeficiency virus infection? Cell Death Differ. 2: 1 – 8

Hengartner M, Ellis R and Horvitz HR (1992) C. elegans gene ted-9 protects ceils from programmed cell death. Nature 356: 494 – 499

Horvitz HR, Sternberg PW, Greenwald IS, Fixsen W and Ellis HM (1983) Mutations that affect neural cell lineages and cell fates during the development of the nematode C. elegans. Cold Spring Harbor Symp. Quant. Biol. **48** pt.2,453-463

Itoh N, Yonehara S, Ishii A, Yonehara M, Mizyshima S, Sameshima M, Hase A, Seto Y and Nagata S (1991) The polypeptide encoded by the cDNA for human cell-surface antigen FAS can mediate apoptosis. Cell **66: 233 – 243**

Ju ST, Panka DJ, Cur H, Ettinger R, El Khatib M, Sherr DH. Stanger BZ and Marshak-Rothstein A (1995) Fas (CD95)/Fas L interactions required for programmed cell death after T-cell activation. Nature 373: 444 – 448

Kerr JFR, Wyllie AH and Currie AR (1972) Apoptosrs: a basic biological phenomenon with wide ranging implications in tissue kinetics. Br. J. Cancer 26: 239 – 257

Knight RA (1995) AIDS: a PCD pathology7 Cell Death Differ. 2: i

Krammer PH (1996) The CD95(APO-1/Fas) receptor/ligand system: death signals and diseases. Celi Death Differ. 3: 159 – 160

Krammer PH (1997) The tumor strikes back: new data on expression of the CD95(APO-1 /Fas) receptor/ligand system may cause paradigm changes in our view on drug treatment and tumor immunology. Cell Death Differ 4: 362-364

Lewis R (1995) Apoptosis activity: Cell death establishes itself as a lively research field. The Scientist Feb 6: 15 – 16

Lockshin RA (1997) The early modern period in cell death. Cell Death Differ. 4: 347-351

Lockshrn RA and Williams CM (1964) Programmed ceil death. II. Endocrine potentiation of the breakdown of the intersegmental muscles of silkmoths. J. Insect Physiol. 10: 643 -649

Lockshin RA and Williams CM (1965a) Programmed cell death. i. Cytology of the degeneration of the intersegmental muscles. J, insect Physiol. 11: 123 – 133

Lockshin RA and Williams CM (1965b) Programmed cell death. iII. Neural control of the breakdown of the intersegmental muscles. J. Insect Physiol. 11: 605 -610

Miyashita T and Reed JC (1995) Tumor suppressor p53 is a direct transcriptional activator of the human bax gene. Cell 80; 293 -299

Murphy KM, Heimberger AB and Loh DY (1990) Induction by antigen of intrathymic apoptosis of CD4+CD8+TCRLO thymocytes in vivo. Science 250: 1720 – 1723

Peter ME, Kischkel FC, Hellbardt S, Chinnaiyan AM, Krammer PH and Dixit VM (1996) CD95(APO-l/Fas)-associating signalling proteins. Cell Death Differ. 3: 161-170

Raff M (1996) Death wish. The Sciences 36,4: 36-40

Saunders JW JR (1948) The proximo-distal sequence of origin of the parts of the chick wing and the role of the ectoderm. J. Exp. Zool. 108: 363 -403

Saunders JW Jr. (1966) Death in embryonic systems. Science 154: 604 – 612

Schwartz LM (1995) The faces of death. Cell Death Differ. 2: 83-85

Sentman CL, Shutter JR, Hockenbery D, Kanagawa 0 and Korsmeyer SJ (1991) bcl-2 inhibits multiple forms of apoptosis but not negative selection in thymocytes. Cell 67: 879 – 888

Small H (1994) A SCI-map case study: building a map of AIDS research. Scientometrics 30: 229 – 241

Small H and Grenlee E (1995) A Co-citation study of AIDS research. In Scholarly Communication and Bibliometrics (CL Borgman ed.) Sage Publications. Newbury Park. pp 166 – 194

Smith CA, Williams GT, Kingston R, Jenkinson EJ and Owen JJT (1989) Antibodies to CD3/T cell receptor complex induce death by apoptosis in Immature T cells in thymic cultures. Nature 337: 181- 184

Stedman's Medical Dictionary, 26th edition. (1995) Williams and Wilkins, Baltimore

Sulston J and Horvitz HR (1977) Postembryonic cell lineages of the nematode ***C. elegans.*** Dev. Biol. 56: 1 10- 156

Tata JR (1966) Requirement for RNA and protein synthesis for Induced regression of tadpole tall in organ culture. Dev. Biol. 13: 77- 94

Trauth BC, Klas C, Peters AMJ, Matzku S, Moller P, Falk W, Debatin K-M and Krammer PH (1989) Monoclonal antibody-mediated tumor regression by induction of apoptosis. Science 245: 301 -305

Williams GT, Smith CA, Spooncer E, Dexter TM and Taylor DR (1990) Hematopoietic colon stimulating factors promote cell survival by suppressing apoptosis. Nature 343: 76 – 79

Wyllie AH (1996) Viruses hold the keys of death. Cell Death Differ. 3: 1 – 2

Wyllie AH (1980a) Glucocorticoid-induced thymocyte apoptosis is associated with endogenous nuclease activity. Nature 284: 555 – 556

Wyllie AH, Morris RG, Smith AL and Dunlop D (1984) Chromatin cleavage in apoptosis: Association with condensed chromatin morphology and dependence on macromolecular synthesis. J. Pathol. 142: 67- 77

Wyllie AH, Kerr JFR and Currie AR (1980b) Cell death the significance of spoptosis. Int. Rev. Cytol. 68: 251 -306

Yonish-Rouach E, Resnitzky D, Lotem J, Sachs L, Kimchi A and Oren M (1991) Wild type p53 induces apoptosis of myeloid leukemic cells that is inhibited by interleukin-6. Nature 352: 345 – 347

Zakeri Z, Bursh W, Tenniswood M, Lockshin RA (1995) Cell death: programmed, apoptosis, necrosis, or other? Cell Death Differ. 2: 87- 96

Cell Death & Differentiation, 4, p.352-361, 1997

ADDENDUM

Our recent report (Garfield and Melino, 1997) elicited considerable interest and comment. This was the first time such an analysis has been conducted in this field. Although we anticipated that the paper was likely to be provocative, we have subsequently become aware of the limitations of the search strategy used to perform the analysis. As a consequence, certain highly cited papers were not selected, including that by Strasser et al (1991). This paper was cited about 500 times and would rank in the 18th place in table 2B. Similarly, the papers by Vaux et al (1994) and Strasser et al (1994) were cited 211 and 138 times, respectively, resulting in a ranking of 2nd and 3rd place respectively in Table 2C. Consequently, there would also be minor adjustments in tables 3 and 4 (most cited authors and organizations).

Any attempt at quantitative analysis of the literature, however sophisticated, must be interpreted by informed judgment. Absolute citation frequencies may be misinterpreted. It was not our intention to judge the significance of the contributions of individual scientists or institutions. We apologize if the work of a few scientists was not appropriately recognized. On the other hand, we are grateful for the interest generated by our paper. It clearly has provoked readers to reflect on the history of apoptosis. We hope to generate an updated analysis in a few years.