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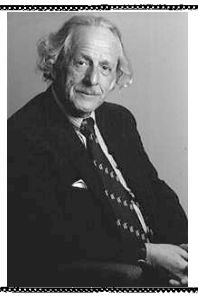

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The Most-Cited 1986 Life-Sciences Articles Highlight Cell-Surface Receptors, Tumor Necrosis Factor, and AIDS Research

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Research-front data on the most-cited 1986 papers reveal trends in hot areas. The most obvious include recombinant DNA technology and cell-surface receptors, human tumor necrosis factor (a potential cancer treatment but also a mediator of shock, cachexia, and inflammation), and the molecular and pharmacological aspects of AIDS. The *Journal of Experimental Medicine* had a good year. Prolific writers such as Bruce Beutler, Robert C. Gallo, and David Baltimore are also well represented.

This essay marks the 11th annual compilation of most-cited life-sciences articles. While citation frequency cannot (and should not) be viewed as the sole indicator of "important" research, this series serves two important functions. First, our analysis helps to identify the "hot" papers that have accumulated a large number of citations in the two years after publication. These papers, having achieved immediate and/or widespread recognition, usually symbolize some scientific milestone, such as a research breakthrough, new methodology, or subject area review. Second, the year-to-year continuities and shifts in research areas often reveal patterns not revealed by the individual papers themselves.

The 103 most-cited papers in the Bibliography can broadly be characterized as involving work in cellular and molecular environment or "ecology." A little less broadly, the papers can be grouped into those on cell receptor research (basic) and those on immunology and pharmacology (applied). The discussion below will embrace several important research areas and show how they are interrelated.

Major Research Trends

Sixty to 70 percent of the papers in the list deal with cell receptors, DNA sequencing and expression, cellular signaling pathways, and other related areas, such as the elements of infection (receptors for infecting organisms such as viruses and retroviruses) and immunology (pharmaceutical factors and immunization).

Tumor Necrosis Factor

About 10 percent of the papers in the Bibliography involve research on an endogenous antitumor mechanism. As described by Lloyd J. Old, Memorial Sloan-Kettering Cancer Center, New York, tumor necrosis factor (TNF) is a mediator molecule, which, with the activation of certain macrophages and the elicitation of an endotoxin, can contribute to the hemorrhagic necrosis of tumors.[1]

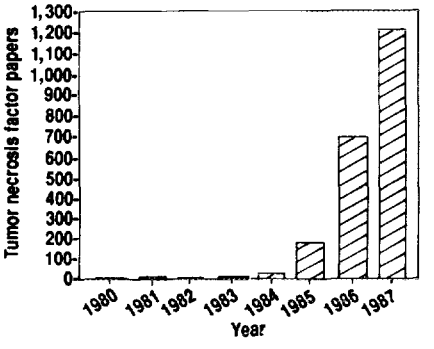
TNF is developing into an extremely active research area, as indicated by the number of papers qualifying for the most-cited list and by the research-front data discussed below. In last year's study (of 1985 life-sciences articles), only a couple of the most-cited papers explicitly dealt with TNF. The references accompanying Old's brief review, mentioned above, are mostly to papers published between 1983 and 1985, however. Actually, the phenomenon of spontaneous regressions of cancer coinciding with bac-

terial infections was noted nearly a century ago by surgeon William B. Coley of New York City. He worked first with bacteria and then with vaccines of killed bacteria (known as "Coley's toxins"), with which he could infect or treat his cancer patients in an attempt to bring about spontaneous regression of the disease.[2]

For decades little was done to pursue Coley's line of inquiry or clinical approach. Again according to Old,[3] there was some research activity in the 1940s at the National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, Maryland, by researchers who identified an active component in tumor necrosis, a compound now called lipopolysaccharide. Then, in 1975, a group of researchers (Old among them) at Sloan-Kettering discovered a small polypeptide, or protein, produced by the body in the course of bacterial infections, which also kills tumors in mice. This was eventually called TNF. The real breakthrough, however, came a decade or so later, when the gene encoding TNF was cloned, the protein's amino-acid sequence was identified, and large amounts of the factor could be produced for study.

Since 1985 there has been an explosion of information about TNF's activities, graphically illustrated in Figure 1, which shows the number of TNF papers indexed in the *Science Citation Index®*. Fewer than 20 papers were published yearly until 1985. With the research milestone mentioned above, the number of papers published in 1985 increased 10-fold. Since then, the dramatic increase has continued. It remains to be seen whether TNF, with the related areas of receptor sites, antigen binding, and pharmacological agents, holds the answer to a cure for cancer. Some of the most-cited papers in the current list, discussed below, seem to suggest just that.

Figure 1: Tumor necrosis factor papers. Year-by-year publication totals for *SCI®* articles with "tumor necrosis factor" or related phrases in their titles.



AIDS Research

As expected, the human immunodeficiency viruses, more popularly referred to as AIDS, are the topic of a large number of papers in the Bibliography (about 20 percent). The surge of papers on various aspects of AIDS—epidemiology, immunology, pharmacology, clinical practice—continues from year to year. From our study of the most-cited 1983 life-sciences articles, published in 1985,[4] to the Bibliography in this study, papers on AIDS-related research have made up a steady 20 to 25 percent of the list. While the numbers have remained the same, the focus of the papers has shifted through the years: from descriptions of the physical manifestations of the disease (before 1983)[5] to the establishment of its viral origin and the isolation of the AIDS viruses (1983 and 1984 papers, dominated by Robert C. Gallo, Laboratory of Tumor Cell Biology, NCI, and Luc Montagnier, Pasteur Institute, Paris, France)[4,6] to the review process and the evaluation of AIDS research (1985 papers)[7] to a focus on both the epidemiology and the immunopharmacology of AIDS in the present list.

Gene Transcription and Cell-Surface Receptors

Aside from the papers focusing on the AIDS viruses specifically, there are about twice as many papers that are related, in varying degrees, to them. This latter group of papers focuses on aspects of molecular biology, especially as it pertains to virolo-

gy, immunology, and a variety of human diseases. These aspects include gene expression and transcription, as well as cell recognition and signaling pathways. Thus, several papers in this group investigate cell-surface receptors—for their potential both in terms of understanding disease processes and of designing drugs to block or regulate the action of destructive gene products.

One such paper, by Y. Yarden, Departments of Molecular and Developmental Biology, Genentech, Inc., San Francisco, California, and coworkers, studies the structure of the receptor for platelet-derived growth factor and relates it to a group of other growth factor receptors, among which is the macrophage colony-stimulating factor.

Another paper, by Nobelists Michael S. Brown and Joseph L. Goldstein, Department of Molecular Genetics, University of Texas Health Science Center, Dallas, reviews a series of studies aimed at unraveling the origin of the genetic disease familial hypercholesterolemia (FH), which involves a very high concentration of cholesterol in the blood leading to heart attacks early in life. After discovering a surface receptor for the plasma cholesterol-transport protein called low-density lipoprotein (LDL) and elucidating this receptor's role in feedback mediation, they demonstrated that FH was caused by inherited defects in the gene encoding the LDL receptor. These defects disrupt the normal regulation of cholesterol metabolism. (For a fuller account of Brown and Goldstein's research, see our 1986 essay occasioned by their winning the 1985 Nobel Prize in physiology or medicine.[8])

The Brown and Goldstein paper illustrates linkage between cell receptor studies (for example, T-cell antigen receptor papers) and gene expression studies. The majority of papers (grappling with AIDS and other diseases) on receptor sites and cellular signaling pose the questions, How do organisms become lethal, and how can they be stopped? A smaller set of papers (dealing with hereditary as well as infectious diseases) on genetic engineering and transcription ask the more primary question, How is a protein (sometimes the signal or the source of the signal to the receptor) built?

Gene transcription papers are concerned with the details of DNA sequencing and how DNA gets transcribed into RNA molecules, which in turn become messenger RNA, which is then translated into protein. These sequences of genetic coding, while generally building orderly products, may occasionally get scrambled or deleted. A product of the painstaking work involved in this type of research is the paper by geneticist Louis M. Kunkel, Children's Hospital, Boston, Massachusetts, and coauthors. Written by 77 authors (a record-breaking number in this series of life-sciences essays), this paper discusses the gene that appears to cause Duchenne muscular dystrophy (DMD). Using recombinant DNA technology, they found evidence of deletions in the genetic code at the DMD locus. (An account of the research and combined results of over 20 research laboratories and of Kunkel's small seven-member team that orchestrated this endeavor was featured in *THE SCIENTIST*® earlier this year.[9]) More papers from the Bibliography in this area of research are mentioned below, in the research-front section.

A particularly interesting paper, by Susan Lindquist, Department of Molecular Genetics and Cell Biology, University of Chicago, Illinois, connects the molecular environment of the cell (signals, messages, and surface receptors) to stress. Proteins released following heat shock are found in all kinds of cellular organisms and, as Lindquist notes, appear to "protect organisms from the toxic effects of heat and other forms of stress."

In general, then, this Bibliography appears to have a number of focal points within the very broad and basic research area of immunology and molecular biology, and especially in the areas of cell receptors and antigen recognition. Among the points are TNF (and growth factors in general), AIDS (and virology research generally), and gene expression and transcription, discussed here, as well as cellular pathology in cardiac disease, protein kinase and calcium, and the

atrial natriuretic factor (the last two areas continuing to be active from last year). The molecular, cellular, and immunological orientation of the majority of the papers suggests a concentration of efforts—all with the hope of finding cures for age-old cancer and modern-day AIDS.

Research Fronts

Table 1 is a list of research fronts in which the most-cited papers figure prominently (research fronts with at least three core papers in the Bibliography). A large number of the papers listed (83 percent) belong to 1987 ISI® research fronts, while 15 percent of the papers are core to 1986 fronts. Additionally, 14 percent of the papers are core to both 1986 and 1987 research fronts (17 percent of the papers in the Bibliography are not associated with any research fronts).

The largest front, #87-1984, "Inositol 1,4,5-trisphosphate, angiotensin-stimulated adrenal glomerulosa cells, and ethanol-induced mobilization of calcium," groups research in the areas of inositol lipid metabolism, intracellular calcium mobilization, and protein kinase C activity. The Bibliography contains three papers that are core to this front—all involving research into the role of inositol phosphates. Two of these are by R.F. Irvine, Institute of Animal Physiology and Genetics Research, Agricultural and Food Research Council, Cambridge, UK, and coauthors.

The earlier paper, which is also the fifth most-cited paper on the list, posits the two-messenger role hypothesis. Irvine's second paper tests the hypothesis and confirms work done elsewhere by Carl A. Hansen, Stephanie Mah, and John R. Williamson, (whose paper is also core to this front), University of Pennsylvania Medical School, Philadelphia. Irvine's work demonstrates that inositol 1,3,4,5-tetrakisphosphate is an intracellular second messenger, whose function it is to control cellular Ca^{2+} homeostasis.

Another large research front, with 1,825 published papers, is "Immunoglobulin heavy-chain gene enhancer, small nuclear ribonucleoprotein particles in pre-messenger

Table 1: The 1986 and 1987 ISI® research fronts that include at least three of the most-cited 1986 life-sciences papers as core documents. A = number of Bibliography papers that are core to each research front. B = total number of core documents. C = total number of citing papers published for the year designated by the prefix.

Number	Name	A	B	C
86-0762	AIDS, heterosexual transmission of AIDS, and HTLV-III infection	3	40	473
87-0070	Fibronectin receptor, adhesion promotion by platelet glycoprotein-IIb/IIIa-like protein in human endothelial cells, and extracellular matrix components	3	36	823
87-0307	Tumor necrosis factor, cultured human endothelial cells, and *in vivo* immune response	8	52	919
87-0629	T-cell antigen receptor complex, surface expression promotion by phorbol 12-myristate 13-acetate, and CD3-associated disulfide-linked gamma-chain heterodimer	3	44	921
87-1208	B-cell stimulatory factor I in B-cell activation, mouse chromosomal gene encoding interleukin-4, and murine assays	3	18	410
87-1678	Immunoglobulin heavy-chain gene enhancer, small nuclear ribonucleoprotein particles in pre-messenger RNA splicing, and tissue-specific expression	4	50	1,825
87-1748	Recombinant murine granulocyte macrophage colony-stimulating factor, regulation of hematopoiesis, and protein tyrosine kinase activity	4	53	1,392
87-1830	HIV, neurologic manifestations of AIDS, and AIDS	3	34	970
87-1984	Inositol 1,4,5-trisphosphate, angiotensin-stimulated adrenal glomerulosa cells, and ethanol-induced mobilization of calcium	3	36	2,251
87-2039	HIV, heterosexual transmission, and AIDS in Africa	3	52	545
87-2296	β_2-adrenergic receptor, regulatory phosphorylation, visual pigments, R7 photoreceptor cell of *Drosophila*, and molecular sites	3	12	385
87-2342	Glucocorticoid receptor, spermine binding-protein gene in mouse ventral prostate, and androgen-regulated expression	4	25	721
87-4459	Protein kinase C and multiple messenger RNA species codes	3	4	175

RNA splicing, and tissue-specific expression" (#87-1678). Papers grouped in this research front are concerned with gene expression and transcription, discussed earlier. Among the core papers are two that are closely linked. The more highly cited of the two (but also published about seven months earlier than the other) is a paper by Harinder Singh, Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology (MIT), Cambridge, and coworkers, on gene promoters. The other paper, on the same topic, is by Ranjan Sen, Whitehead Institute for Biomedical Research, Cambridge, Massachusetts, and David Baltimore, Department of Biology, MIT—both coauthors on Singh's paper. Both papers study transcriptional regulatory elements that interact with immunoglobulin enhancer sequences. Several of these binding proteins were identified, the most important being a human B-cell nuclear factor. Incidentally, Baltimore was awarded the Nobel Prize in physiology or medicine in 1975, together with Howard Temin, University of Wisconsin, Madison, another coauthor (see J. Coffin's paper) in the Bibliography.

Worth noting, too, are three fronts on AIDS. Two of these, "AIDS, heterosexual transmission of AIDS, and HTLV-III infection" (#86-0762) and "HIV, heterosexual transmission, and AIDS in Africa" (#87-2039), are closely linked—their subject being the epidemiology of AIDS and public-health concerns, such as transmission and testing. These two fronts have 29 core papers in common, constituting 46 percent of their combined core papers, 3 of which appear in the Bibliography. A review by Robert J. Biggar, International AIDS Epidemiology, Environmental Epidemiology Branch, NCI, reports on the extent of our knowledge of the epidemic in Africa. Similarly, the paper by John K. Kreiss, Harborview Medical Center, Seattle, Washington, and coworkers reports on the alarming spread of AIDS from central to eastern Africa, as indicated by the screening of several populations in Nairobi, Kenya. More reassuring is a study by Gerald H. Friedland, Montefiore Medical Center, Bronx, New York, and coauthors of nonsexual household contacts. Based on interviews, physical examinations, and blood tests, this last study concludes that there is minimal or no risk of infection in such a context.

The third front on AIDS, "HIV, neurologic manifestations of AIDS, and AIDS" (#87-1830), groups papers that are more heavily biotechnical. The three core papers in the Bibliography, all published in *Science*, are concerned with the *in vitro* study of certain cell or molecule characteristics that can explain the pathogenesis of AIDS. The earliest and most highly cited of the three, by J.S. McDougal *et al.*, Immunology Branch, Centers for Disease Control, Atlanta, Georgia, investigates the possibility of the T4 molecule being a virus receptor. Among other findings, the investigators noted that viral glycoprotein 110 bound to the T4 molecule. Indeed, such findings are already leading to potentially useful therapeutic as well as preventive measures (vaccines) against AIDS.[10]

The other two papers both deal with the role of phagocytes in AIDS. The paper by Suzanne Gartner, Laboratory of Tumor Cell Biology, NCI, and coworkers evaluates cells with properties characteristic of mononuclear phagocytes. Results suggest that these may serve as primary targets for infection and agents for virus dissemination. The second paper, by Scott Koenig, National Institute of Allergy and Infectious Diseases, NIH, and coauthors, carries this line of research further. In an attempt to explain neurological complications common to AIDS patients, and with the help of techniques such as cocultivation for virus isolation, *in situ* hybridization, and transmission electron microscopy, the authors identified a cell type that supports replication of the AIDS retrovirus in brain tissue. The cell type, like that isolated by the Gartner team, was a macrophage that synthesized viral RNA.

The representative papers on AIDS discussed here illustrate how far our knowledge of AIDS has advanced. Human retroviruses, which were hypothetical entities less than a decade ago, are now an area of burgeon-

ing research, with clinical application not far off.

Most-Cited Papers/Authors

The top papers in this study form a heterogeneous group, which is to be expected in the multi- and interdisciplinary research areas of the life sciences. The most-cited paper in the Bibliography is a review article by Yasutomi Nishizuka, Kobe University School of Medicine, Japan, on protein kinase C. *Current Contents®* readers may recall that, in our essay on the most-cited 1984 life-sciences articles,[6] Nishizuka was also at the top of the list with a similar review. His 1984 review had accumulated some 500 citations in a two-year period. However, the 1986 paper has accumulated only about 300 citations in roughly the same period. Also, the 1984 review was core to research fronts (in 1984 and 1985). The 1986 paper has not yet identified a particular 1986 or 1987 front. However, the 1984 paper has—#87-1984, discussed earlier. This might mean that while the topic was new and very active in 1984-1985, it has stabilized. Perhaps next year's co-citation clustering will pick it up as a core work. It is normal to expect an up-to-date review to supercede an earlier one.

Nishizuka's 1986 review elaborates on the properties and possible roles of protein kinase C. One of the novel functions of this protein kinase system, brought to light in recent studies, appears to be related to the feedback control of cell surface receptors, termed "down-regulation." The author provides several useful tables outlining roles and substrates of protein kinase C and interweaves his lengthy bibliography with the tabular data. Finally, all the available evidence continues to suggest a crucial role for this enzyme in signal transduction, both for the activation of many cellular functions and for the control of cell proliferation.

Another highly cited review paper (third from the top) is by Russell Ross, Department of Pathology, University of Washington, Seattle. It describes research on the cellular composition of atherosclerotic lesions and emphasizes the interactions among the cells involved in lesion formation. This paper is yet another illustration of laboratory studies interacting with clinical practice.

In addition, there is an interesting set of eight papers explicitly on TNF, all of which are core to research front #87-0307, "Tumor necrosis factor, cultured human endothelial cells, and *in vivo* immune response." Bruce Beutler (formerly at the Laboratory of Medical Biochemistry, The Rockefeller University, New York, and now at the Howard Hughes Medical Institute, University of Texas Health Science Center, Dallas) appears as primary author of six core papers in this front. One of these, coauthored by Anthony Cerami, also of The Rockefeller University, and editor, *Journal of Experimental Medicine*, is the fourth most-cited paper in the Bibliography. This review paper describes the hormonal substance cachectin, which is secreted by macrophages and travels via the circulatory system to distant sites in the body, where it binds to specific receptors and exerts discrete metabolic effects. Prominent among its biological effects is its ability to induce wasting (cachexia) and a lethal state of shock. As mentioned earlier, cachectin (TNF) has been produced on a large scale for use in trials as an antineoplastic agent. Studies are also under way to characterize the TNF receptor and may lead to the development of specific blocking agents.

More recently, Beutler has contributed a brief exposition of research on TNF to the *ISI Atlas of Science®: Immunology*. After reviewing the background of this research area and its current status, Beutler concludes that "a thorough understanding of the role played by cachectin in the immune system might be tantamount to an understanding of the role of inflammation itself. In the future, it is expected that a grasp of the beneficial effect of cachectin will be gained and that means will be found to antagonize production of the hormone or its action in vivo."[11]

Four of the papers on TNF were published in the *Journal of Experimental Medicine*. This ranks it in the top five life-sciences

journals, returning it to its performance of half a decade ago. Its higher (than in recent years) representation here confirms our previous assessment of it as a "journal *extraordinaire*."[12] Among them are two related papers by Peter P. Nawroth, Oklahoma Medical Research Foundation, Oklahoma City, and colleagues on TNF and endothelial cell receptors. The first paper reports the results of an experiment with bovine aortic endothelial cells, which, when incubated with recombinant TNF, show enhanced procoagulant activity. The second, using cultured human umbilical vein endothelial cells, found that these cells possess binding sites for TNF. This study also found that the interaction of TNF with endothelium leads to the synthesis and release of interleukin 1. From both studies, the authors suggest that TNF can initiate a "cascade of inflammatory events."

It should also be added that several of the papers in the Bibliography deal with members of the group of soluble growth- or behavior-modifying factors now called cytokines (formerly, lymphokines), for example, the paper by Timothy R. Mosmann, DNAX Research Institute of Molecular and Cellular Biology, Inc., Palo Alto, California, and coworkers. These range from TNF and interleukins to colony-stimulating factors and interferons. The relationship of these areas is still unclear to many—perhaps because they constitute a still-emerging story.[13] David W. Galvani, Royal Liverpool Hospital, UK, reviewed these interrelated topics recently.[14]

Thus, the picture that emerges from all the papers and research fronts presented earlier is one of furious research activity—in recombinant DNA and RNA, in cell-surface receptors, in protein kinase C and cellular signaling, in TNF and its therapeutic potential, and, lastly, in AIDS-related social, clinical, and biochemical problems.

Author, Journal, and Country Profiles

None of the essays in this series would be complete without drawing attention to the peculiarities or anomalies the data reveal.

Table 2: The number of authors per paper for the 1986 life-sciences articles most cited in the *SCI®*, 1986-1987.

Number of Authors per Paper	Number of Papers
77	1
18	1
16	1
15	1
14	2
13	2
12	3
11	5
10	2
9	2
8	3
7	9
6	12
5	9
4	11
3	11
2	13
1	15

Aside from the authors and papers already mentioned in the course of this discussion, a few more deserve mention. For instance, Gallo, a prolific author and AIDS researcher, again shows up as the top coauthor (with five papers) on the list. For the past five years, he has been the top coauthor in this series.

Also evident from the data in Table 2 is that, on average, the number of authors per paper is six. This, however, is skewed by the 77 authors on the Kunkel paper, mentioned earlier. When this paper is removed, the average number of authors per paper falls to 5.4, which is slightly below the average for recent years (5.6 for 1985 and 5.8 for 1984 life-sciences papers).

The journal representation in the Bibliography (see Table 3) is generally what would be expected—with *Nature* and *Science* accounting for 52 percent of the papers, followed by *Cell* and the *New England Journal of Medicine*. Unusual is the position of the *Journal of Experimental Medicine*, with four papers in the Bibliography—when in the four previous years it published at most two papers that qualified for the most-cited papers for the year. It will be interesting to look for the journal in the most-cited 1987

Table 3: The 21 journals that published the papers listed in the Bibliography. The numbers in parentheses are the 1986 impact factors for the journals. (The 1986 impact factor equals the number of 1986 citations received by the 1984-1985 articles in a journal divided by the number of articles published by the journal during that same period.) Data were taken from the 1986 *JCR®*. The figures at the right indicate how many papers from each journal appear in the Bibliography.

Journal	Number of Papers
Nature (15.3)	29
Science (12.4)	25
Cell (20.1)	10
N. Engl. J. Med. (17.8)	7
J. Exp. Med. (10.9)	4
Lancet (12.9)	4
Proc. Nat. Acad. Sci. USA (9.2)	4
Annu. Rev. Biochem. (31.6)	2
Annu. Rev. Immunol. (26.5)	2
Biochem. J. (4.2)	2
Blood (6.2)	2
J. Biol. Chem. (6.3)	2
Trends Biochem. Sci. (5.0)	2
Anal. Biochem. (2.5)	1
Annu. Rev. Neurosci. (15.4)	1
Ca—A Cancer J. Clin. (4.5)	1
Cancer Res. (4.1)	1
EMBO J. (8.1)	1
Immunol. Today (6.9)	1
J. Immunol. (6.2)	1
Pharmacol. Rev. (15.3)	1

Table 4: National locations of the institutional affiliations listed by authors in the Bibliography, according to total papers (column A). B=number of papers coauthored with researchers affiliated with institutions in other countries. C=national locations of institutions listed by coauthors.

Country	A	B	C
US*	94	7	FRG, Israel, Japan
UK*	6	2	US
Japan	5	2	Sweden, US
France*	4	3	Israel, US
Israel	2	2	France, US
Australia*	1	1	
Canada*	1	1	
Finland*	1	1	
FRG	1	1	US
GDR*	1	1	
Italy*	1	1	
The Netherlands*	1	1	
Sweden	1	1	Japan

* Appeared on Kunkel L M. *Nature* 322:73-7, 1986, a collaboration between authors from Australia, Canada, Finland, France, the GDR, Italy, The Netherlands, the UK, and the US. This collaborative group is not listed in column C.

papers next year—to determine whether its 1986 representation is a new trend in that journal's publishing profile or if it is a coincidence related to the activity in TNF, the subject of the four papers.

Finally, Table 4 lists the countries, 13 in all, represented by the most-cited papers—with the US predictably on top, with 94 papers. Switzerland, third in the 1985 Bibliography with six papers, is not on the list of 1986 published papers. Japan is represented by five papers—the same number as in the 1985 list. Of the 134 unique institutions represented, there are 4 with six or more authors on the list—all with US affiliations. The NIH leads the list, appearing 12 times. Eight of these research efforts were from the NCI division. Harvard appears 11 times (Harvard Medical School, University, and School of Public Health). Finally, the University of California (the San Francisco campus appears five times and the Berkeley campus, twice) and Yale University, New Haven, Connecticut, are represented seven and six times, respectively.

Conclusion

The rate of citation accumulation, particularly in the life sciences, may warrant special comment. It is not unusual nowadays for a research paper to qualify as a *Citation Classic®* in much less time than it used to take. Indeed, many recent ones are barely four years old with well over 1,000 citations.[15,16] Undoubtedly this has something to do with the advances in the technology of information storage and dissemination. Examples of this technology can be seen in the automation of indexing and information retrieval, in faster and cheaper telecommunication lines, and in the electronic manipulation and saving of data. However, it also has something to do with the nature of modern society and its unique response to the medical realities it is confronted with. What I am suggesting is that the speed and amount

of scientific publications has to do with the social and medical urgency of the main areas under study—AIDS, cancer, and the human immune system.

AIDS, as the truism goes, has reached epidemic proportions. This is attested by the speed with which researchers learn about and cite other investigators (even before a paper is published[17]). Knowledge of experiments and results is being disseminated—at conferences, through the mass media, and through personal or scholarly correspondence.

I am reminded of the comments of Lewis Thomas, former president of Memorial Sloan-Kettering Cancer Center, on the motivations of scientists to explore and to relate their discoveries:

> It is fascinating that the word "explore" does not apply to the searching aspect of the activity, but has its origins in the sounds we make while engaged in it. We like to think of exploring in science as a lonely, meditative business, and so it is in the first stages, but always, sooner or later, before the enterprise reaches completion, as we explore, we call to each other, communicate, publish, send letters to the editor, present papers, cry out on finding.[18]

* * * * *

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