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Cell Signaling, the Immune Response, the Genetic Basis of Cancer, and Efforts to Pinpoint the Genes for Alzheimer's Disease, Cystic Fibrosis, and Manic-Depressive Illness Are Highlighted in 1987 Life-Sciences Research

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At least a quarter of the 101 most-cited 1987 papers were devoted to various aspects of communication between cells and the translation of such signals into metabolic activity. In addition to this burgeoning research field, the 1987 listing was notable for including papers on the putative genes for Alzheimer's disease, cystic fibrosis, and manic-depressive illness. These were heavily cited in part because the claims were subsequently invalidated to some degree. The US tally of papers has declined, while the UK share has risen sharply.

The most striking attribute of the life sciences today is the way in which methods such as gene mapping and cloning, derived from the molecular biology revolution of the 1960s and 1970s, are now transforming the entire spectrum of life sciences, from immunology to neurosciences, from medical diagnostics and screening to cancer research. This is clearly illustrated by the 12th annual compilation of most-cited life-sciences papers, identified through the ISI® database. The 101 top papers of 1987 confirm that not only the techniques but also the concepts of molecular biology now form the central axis for biological research.

Although key areas such as cell signaling emerge forcibly from this study, by sheer weight of numbers, several other highlights of the year concern claims in highly competitive sectors of medical science in which the original hopes were not fulfilled.

Cell Signaling

One of the most phrenetic research fields in recent years has been the identification of the messengers and mechanisms involved in communication between and within cells. This is reflected in four of the top seven most-cited papers and in at least a quarter of the top 101 communications (several others touch on the subject). All address different aspects of a chain of events that begins with a "first messenger" (hormone or neurotransmitter) acting on a receptor on the surface of a cell and triggering the generation of a "second messenger" that sets the cell's response in motion. The signal is amplified in the production of the second messenger, often by means of an intermediate group of proteins called signal transducers. In other cases the first messenger works by opening up an "ion channel," and the degree of amplification depends on the number of ions that flow into the cell while each channel is open.

The most-cited paper, with over 280 citations, is that in which Alfred G. Gilman, Department of Pharmacology, University of Texas Health Science Center, Dallas, reviewed one group of signal transducers, the G proteins, and proposed a tighter definition than had been possible hitherto. Another review, by Michael J. Berridge, Unit of Invertebrate Physiology and Pharmacology, Agricultural and Food Research Council, Cambridge, UK, was the fifth most-cited paper. He discussed ways in which the two principal second messengers, diacylglycerol and inositol trisphosphate, interact with each other in regulating many different types of cells. Last year Berridge authored a *Citation Classic*® essay on a 1975 paper on second messengers.[1]

Eleven papers were devoted to ion channels, although the systems under study

varied widely. For example, J. Hescheler, Saar University, Federal Republic of Germany (FRG), and coworkers investigated the opiate receptor and extended our understanding of the way in which opioid peptides and opiates inhibit the release of neurotransmitters in nerve cells. Tsutomu Tanabe, Kyoto University Faculty of Medicine, Japan, and coworkers reported the cloning of the receptor in rabbit skeletal muscle for dihydropyridine, which may act as a calcium ion channel involved in muscle contraction. And in a notable case of "dogma disproved," Diomedes E. Logothetis, Harvard Medical School, and colleagues showed that the "wrong" subunit regulated potassium channels in heart cells. Together with the paper by Atsuko Yatani *et al.*, Baylor College of Medicine, Houston, Texas, this was an important advance in our understanding of the molecular basis of the regulation of heart rate.

A particularly intriguing question was addressed in the paper by Shigeo Ohno, Tokyo Metropolitan Institute of Medical Science, Japan, and colleagues. On the basis of studies with protein kinase C (which can be activated in the cell by diacylglycerol) they helped to show how a limited portfolio of signaling substances can generate such a wide diversity of messages.

Peter Angel, Institute for Genetics, University of Karlsruhe, FRG, and colleagues studied signaling of a different sort. They helped to uncover the complex chain of events by which tetradecanoyl-phorbol-acetate, a potent tumor inducer that potentiates the effect of subcarcinogenic doses of carcinogen, affects gene transcription in the cell.

Work at INSERM's Molecular Biology and Genetic Engineering Group in Strasbourg, France, focused on retinoic acid—which, like its parent substance vitamin A, is required for the control of endothelial cell growth and for cellular differentiation. Martin Petkovich, Nigel J. Brand, Andrée Krust, and Pierre Chambon reported their identification of the retinoic acid receptor as a member of the steroid/thyroid receptor family.

Cell Adhesion

The second-ranking paper, with approximately 250 citations, is that in which Richard O. Hynes, Massachusetts Institute of Technology (MIT), Cambridge, surveyed our rapidly evolving picture of the way in which cells adhere together and migrate through the extracellular matrix. Investigations into these processes and into phenomena such as thrombosis have revealed close similarities between receptors for matrix proteins on cell surfaces, glycoproteins on platelets (which play a key role in thrombosis), and surface components of lymphoid cells. This has led to the recognition of a new family of cell surface receptors called integrins. They interact with matrix proteins and other cells, participating not only in adhesion but also in thrombosis, wound healing, and immune defense mechanisms.

In their paper, Erkki Ruoslahti and Michael D. Pierschbacher, Cancer Research Foundation, La Jolla, California, discussed the structures of matrix proteins, their receptors in normal and abnormal cells, and the tripeptide arginine-glycine-aspartic acid, which many of them contain and which plays a key role in adhesion. A new "supergene" family of adhesion proteins was defined in the report by Takashi K. Kishimoto and coworkers at the Dana-Farber Cancer Institute, Boston, Massachusetts.

The Immune Response

The adhesion of cells is also important when an animal defends itself against infection—for example, when a T lymphocyte attacks an invading bacterium. The paper by Kishimoto and that by Timothy A. Springer *et al.*, also of the Dana-Farber Cancer Institute, deal with interactions between lymphocyte receptors and proteins outside the cell. In turn they fall into a group of 23 papers all covering some aspect of the immune response. Four of these are specifically concerned with T-cell receptors. Particularly noteworthy are the papers, published in the same issue of *Nature*, in which Jannie Borst, The Netherlands Cancer Institute, Amsterdam, and colleagues and

Michael B. Brenner, Dana-Farber Cancer Institute, with colleagues made an important advance in understanding the structural basis of immune recognition—an advance that could also have practical value. They definitively identified several T-cell receptors that differed fundamentally from what can now be termed the "classical" receptors reported three years earlier. Although representing under 5 percent of T-cell receptors in the cells in peripheral blood, the newly identified receptors have a broader specificity.

These receptors also differ in apparently not being prevented from recognizing antigens unless they are associated with the major histocompatibility complex (MHC) on the surface of cells. In two other highly cited papers, P.J. Bjorkman, Department of Biochemistry and Molecular Biology, Harvard University, and coworkers reported the three-dimensional structure of the binding site of the MHC molecule HLA-A2. Thirteen years after the first discovery of MHC-restricted recognition, this helped immunologists to begin to comprehend the structural basis of key events in the immune response.

Soren Buus and a team at the National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado, reported studies on MHC restriction that shed further light on the central problem of immunology—how the body can manufacture specific antibodies to match an infinite number of different antigens, yet not attack "self." This theme was developed in an associated paper by Jean-Gerard Guillet, Department of Biology, MIT; Buus; and coworkers. John W. Kappler, also at the National Jewish Center for Immunology and Respiratory Medicine, and others showed how animals become tolerant to "self-MHC" because certain lines of T cells are eliminated during their maturation in the thymus gland—rather than (as proposed previously) because activation of these clones had been prevented.

Bruce Beutler and Anthony Cerami, Laboratory of Medical Biochemistry, The Rockefeller University, New York, and University of Texas Health Science Center,

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logged only 13 less citations than their 1986 score of 181[2] for a paper in which they reviewed our knowledge of cachectin. Originally discovered during research into cachexia (the wasting and emaciation seen in some cancer patients), this substance is now known to have many other actions, including the eliciting of shock and hemorrhagic necrosis. Another highly cited review was that in which Steven C. Clark and Robert Kamen, Genetics Institute, Inc., Cambridge, Massachusetts, discussed granulocyte colony-stimulating factor, macrophage colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and interleukin-3. The genes for these factors have all been cloned in recent years, leading to large-scale production by recombinant DNA technology. Clinical applications are now emerging.

AIDS and Human Immunodeficiency Virus

Nine papers were specifically devoted to AIDS and its virus(es). Mireille Guyader and colleagues (including Luc Montagnier, codiscoverer of the human immunodeficiency virus [HIV]) at the Pasteur Institute, Paris, France, reported the nucleotide se-

quence of HIV-2, which is associated with AIDS in Africa. Although biologically similar to HIV-1, commonly found in AIDS cases in Western countries, the two organisms proved to be evolutionarily distinct. It seems that both viruses existed long before the present epidemic.

Gary Nabel and 1975 Nobel laureate David Baltimore, Whitehead Institute for Biomedical Research, MIT, reported on the expression of HIV in T lymphocytes. B. Frank Polk, Johns Hopkins University School of Medicine, Baltimore, Maryland, and colleagues at six other US centers described markers (such as decreased numbers of T helper lymphocytes) that are significantly linked with progression from HIV infection to AIDS proper. Likewise, Jonathan N. Weber, Chester Beatty Laboratories, Institute of Cancer Research, London, with collaborators at four UK institutions, monitored the development of the disease in relation to changing antibody levels.

The most-cited AIDS paper (with over 140 citations) was that in which Margaret A. Fischl, University of Miami School of Medicine, Florida, and colleagues (including members of the AZT Collaborative Working Group) reported a double-blind placebo-controlled trial showing that the administration of azidothymidine (AZT) decreased mortality and opportunistic infections in some patients with AIDS or AIDS-related complex, at least in the short term. Fischl was also the first-named author of a paper on contacts and partners of AIDS patients. But the second most-cited AIDS paper, printed in the same issue of the *New England Journal of Medicine*, was that in which essentially the same team (with Douglas D. Richman, University of California, San Diego [UCSD], as first-named author) showed that, while some patients tolerated AZT well, the drug should be administered with caution because of its toxic effects.

The other AIDS papers were a review of means of attacking the virus, by Hiroaki Mitsuya and Samuel Broder, National Cancer Institute (NCI), Bethesda, Maryland, and a report on the use of genetically engineered human granulocyte-macrophage colony-stimulating factor to restore white blood cell counts in AIDS patients, by Jerome E. Groopman, New England Deaconess Hospital, Boston, and colleagues.

The Genetic Basis of Cancer

The third most highly cited paper of 1987, with 230 citations, was that in which 1989 Nobel laureate J. Michael Bishop, University of California Medical School, San Francisco (UCSF), reviewed our evolving knowledge of the origin of cancer in cellular DNA—a field in which he has made many major contributions. Bishop focused largely on oncogenes, which seem to be required for normal growth and development but which have the potential to cause malignancy. A paper by Johannes L. Bos, Department of Medical Biochemistry, State University of Leiden, The Netherlands, and coworkers showed that mutations of *ras* genes (also reviewed in the paper by Mariano Barbacid, Developmental Oncology Section, Frederick Cancer Research Facility, Maryland) were present in over a third of human colorectal tumors, usually occurring before the appearance of cancer.

Amplification of another oncogene was linked to relatively rapid relapse of primary breast cancer, and shorter survival times, in a paper by Dennis J. Slamon and a team from the University of California School of Medicine, Los Angeles (UCLA). The papers of Dirk Bohmann, Department of Biochemistry, UCLA, *et al.*; Kathleen Forrester, Department of Biochemistry, State University of New York, Stony Brook, *et al.*; and E. Solomon, Somatic Cell Genetics Laboratory, Imperial Cancer Research Fund, London, *et al.*, describe other gene changes associated with malignancy.

In their report from the Department of Pathology, UCSD, Wen-Hwa Lee and collaborators described the identification, cloning, and sequencing of the putative gene for retinoblastoma, a condition in which tumors grow in the eyes of children. Their work

provides a framework for studying other recessive genetic mechanisms in human cancers.

Two papers dealt with advances in cancer treatment. In the fourth-placed paper (over 210 citations), Steven A. Rosenberg and a team at NCI described the use of an immune modulator, interleukin-2, in patients with advanced kidney, lung, or other cancers that were metastasizing to other parts of the body and could not otherwise be treated. Lymphocytes were taken from patients, incubated with interleukin-2, and the resulting "lymphokine-activated killer cells" reinfused, together with interleukin-2, back into the patients. Of 106 subjects, eight responded completely (measurable tumor disappearing totally). Another 15 responded partially, and 10 to a lesser degree. Concurrently, William H. West and colleagues at the Biological Therapy Institute, Memphis, Tennessee, reported that interleukin-2 administered as a continual infusion to treat kidney, colon, and other cancers was as effective as, but more comfortable for the patient than, earlier methods of giving the drug.

Alzheimer's Disease

Four papers with over 130 citations each focused on Alzheimer's disease (formerly known as senile dementia). Jie Kang, Institute for Genetics, University of Cologne, FRG, and colleagues pinpointed the gene responsible for the A4 polypeptide that occurs in the amyloid plaques seen in the brain in patients with this disease. Interestingly, they located the gene on chromosome 21—the one that causes Down's syndrome when it is present in triplicate.

These findings were extended in a paper from the National Institute of Neurological and Communicative Disorders and Stroke, NIH. Dmitry Goldgaber was first-named author and the other signatories included D. Carleton Gajdusek, Nobel Prize winner in 1976 for his work on the transmission of kuru among the Fore people in New Guinea. This paper and another by Rudolph E. Tanzi, Harvard Medical School, and colleagues described the isolation, cloning, and characterization of the DNA that codes for amyloid.

In the fourth paper, with Tanzi as second-named author, Peter H. St George-Hyslop, Harvard Medical School, with US, Italian, French, and German collaborators used the DNA to determine where the amyloid gene was expressed in the brains of Alzheimer's disease and Down's syndrome patients and to map the gene on chromosome 21.

But suspicions that the amyloid gene was *the* Alzheimer's disease gene proved to be very short-lived. Before the end of 1987, papers appeared by the Tanzi and St George-Hyslop groups,[3,4] and by researchers at the University of Antwerp, Belgium,[5] showing that the disease did not seem to segregate together with the amyloid gene in affected families. Although certainly involved in the condition, the amyloid gene was "the wrong gene in the right place at the right time."[6] One reason for the high ratings of the four earlier papers, therefore, was that they were cited in these and other reports that in effect repudiated the implications of the previous findings and set them in perspective.

Cystic Fibrosis

A similar "near miss" registered by a heavily cited paper of 1987 was the announcement by Xavier Estivill and other members of Bob Williamson's team at St. Mary's Hospital Medical School, London, of a candidate for the gene that causes cystic fibrosis (CF). They had cloned and characterized a DNA sequence very close to the CF locus on chromosome 7. But within a few months, it became clear that this was not the actual gene responsible for the disease. That was pinpointed over two years later, in September 1989, by researchers at the University of Toronto, Ontario, Canada; the Hospital for Sick Children, Toronto; the Frederick Cancer Research Facility; and the University of Michigan, Ann Arbor.[7] Identification of the gene has led to the development of DNA probes for screening carriers, although these are not yet capable of detecting 100 percent of carriers because some

mutations in the gene remain to be characterized.

Manic Depression

A third "breakthrough" of 1987 that subsequently turned out to have been premature was an apparent demonstration of the genetic basis of a mental illness by Janice A. Egeland, University of Miami School of Medicine, and colleagues. They published strong supporting evidence for their claim of two years previously that manic-depressive disease among the Old Order Amish of Pennsylvania was traceable to a single dominant gene on the short arm of chromosome 11, which conferred a strong predisposition to this condition.

But this was indirect evidence. The gene concerned was not positively identified, but implicated because it seemed to be coinherited with two marker genes (the insulin gene and the Harvey-*ras*-oncogene). The argument therefore hung on a statistical calculation of the unlikelihood of this coinheritance occurring by chance. Since then, two individuals in the original Amish pedigree have developed manic depression in the absence of the supposed markers, while a lack of linkage has been reported in other branches of the pedigree.[8] Perhaps two genes are at work. Perhaps the original implication of a gene on chromosome 11 *was* a result of pure chance. Time will tell.

Other Highlights

In their sixth-placed paper, Tom Maniatis, Stephen Goodbourn, and Janice A. Fischer, Department of Biochemistry and Molecular Biology, Harvard University, reviewed their work in identifying and characterizing certain DNA sequences required for gene regulation in eukaryotic cells. Maniatis also coauthored a paper with Robin Reed, also of Harvard's Department of Biochemistry and Molecular Biology, describing a class of short RNA molecules, complexed with protein, that are found in the nuclei of higher eukaryotic cells and form part of the machinery whereby RNA transcripts are processed into their functional form. This work should further our understanding of how specific genes are expressed at different times, in particular tissues, and in response to inducers from outside the cell.

Applications of molecular biology were recorded in several other papers. Joseph W. Eschbach, Department of Medicine, University of Washington, Seattle, showed that human erythropoietin made by recombinant DNA technology corrects the anemia associated with chronic kidney failure and can eliminate the need for blood transfusions in patients undergoing hemodialysis. Very recently, the same drug has been found to be highly effective in treating porphyria cutanea tarda in long-term dialysis patients, too.[9]

Judah Folkman and Michael Klagsbrun of Children's Hospital, Boston, and Harvard Medical School, surveyed the "hot" field of angiogenesis. This is the formation of new capillary blood vessels, a phenomenon that accompanies wound healing, ovulation, tumor growth, and many other normal and pathological processes. The isolation of "angiogenic factors" and the cloning of the appropriate genes, as reported in this paper, should lead to an understanding of how the process is normally kept under control.

In their paper R.M.J. Palmer and collaborators at the Wellcome Research Laboratories, Beckenham, UK, seem to have solved the long-standing problem of how endothelial cells react to mechanical stress, and to various neurohormonal mediators, by releasing substances that help to either constrict or widen blood vessels. They identified one of the most powerful of these substances, formerly called endothelium-derived relaxing factors, as nitric acid. Salvador Moncada, one of Palmer's coauthors, has written two *Citation Classics* essays on earlier highly cited papers.[10,11]

A marked improvement in two Parkinson's disease patients following the grafting into the brain of dopamine-producing tissue taken from the patients' own adrenal glands was announced in the report by Ignacio Madrazo and a team at the National Autonomous University of Mexico, Mexico City. More recently, doubts have been expressed

Table 1: The 1987 and 1988 ISI® research fronts that include at least three of the most-cited 1987 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
87-0926	Neuritic plaque amyloid fibrils in Alzheimer's disease, distal end of mouse chromosome 16, and anti-beta protein monoclonal-antibody	4	20	335
87-6630	K^+ channels, guanine nucleotide-binding regulatory proteins, muscarinic receptor mediated stimulation, pertussis toxin, cell calcium, and brain membranes	3	3	69
88-0256	Gamma-delta T-cell receptor genes in human T-cell precursors, somatic generation of immune diversity (Nobel lecture), and surface expression	8	51	1,007
88-0412	Guanine nucleotide-binding regulatory subunits, ion channels, and immunocytochemical localization	4	29	892
88-0556	T-cell activation, malaria circumsporozoite protein, antigen processing, synthetic peptide-based vaccine, and MHC molecules in determinant selection	4	37	805
88-0877	Laminin receptors, integrin family, extracellular-matrix proteins, sequence homology, human lymphocyte-T activation, and sites of transmembrane interaction	3	52	1,492
88-0963	Senile plaques in Alzheimer's disease, cerebral amyloid angiopathy, precursor protein, and differential expression	4	49	1,046
88-1020	Proto-oncogene *fos* transcription, common *trans*-acting factor, mouse fibroblasts, expression of the SV40 promoter, *in vitro* activation, and phorbol ester	5	32	1,225
88-1041	Excitatory amino-acid receptors, n-methyl-d-aspartate responses of mouse central neurons, NMDA antagonists, and rat retinal ganglion cells *in vitro*	4	39	705
88-1259	Glucocorticoid receptor DNA-binding domain, transcriptional activation of the rat prolactin gene, and avian erythroblastosis virus v-*erb*-A oncogene	3	40	1,193
88-1514	Human immunodeficiency virus type-1, anti-HIV activity, antiviral agents, and 3′-azido-3′ deoxythymidine (AZT)	3	26	404

about the long-term benefits of this therapy in the majority of patients.[12]

Research Fronts

Table 1 shows the 11 ISI research fronts for 1987 and 1988 whose "core documents" include at least three of the most-cited 1987 life-sciences papers. Particularly conspicuous, with eight of these papers in the core, is #88-0256, "Gamma-delta T-cell receptor genes in human T-cell precursors, somatic generation of immune diversity (Nobel lecture), and surface expression." This reflects the relationship between research into two topics discussed above—T-lymphocyte receptors and the capacity of the body to generate an infinite number of different antibodies following exposure to foreign antigens. T-cell research figures in two other fronts. It is linked with malarial parasites, MHC, and synthetic peptide vaccines in #88-0556, and with integrins and intracellular proteins in #88-0877. Two research fronts, #87-6630 and #88-0412, deal with ion channels, while #87-0926 and #88-0963 both embrace papers on the amyloid plaques seen in the brains of patients with Alzheimer's disease.

Authors

For five years in succession, 1982-1986 inclusive, AIDS researcher Robert C. Gallo, Laboratory of Tumor Cell Biology, NCI, was the coauthor with more papers to his

Table 2: The number of authors per paper for the 1987 life-sciences articles most cited in the *SCI®*, 1987-1988.

Number of Authors per Paper	Number of Papers
22	1
14	2
13	3
12	1
11	3
10	3
9	3
8	8
7	6
6	10
5	11
4	10
3	5
2	20
1	15

credit in this series than any other author. His name appeared on five of the 1986 papers reviewed in 1988.[2] Gallo does not figure in the 1987 listing, in which the most prolific author is Robert Tjian, University of California, Berkeley. Tjian coauthored five papers on various aspects of cell signaling and transcription factors—those first-authored by UCLA's Bohmann and other University of California, Berkeley, colleagues Katherine A. Jones, Wes Lee (two papers), and Pamela J. Mitchell.

There were three Nobelists—Baltimore, Bishop, and Gajdusek, each of whose work is discussed earlier. When Bishop was honored last year with Harold E. Varmus, UCSF, former colleague Dominique Stéhelin, now director of research, National Scientific Research Center, Lille, France, complained that he should have shared the prize, and the controversy still continues.[13,14] Beutler and Cerami appeared in the list for the second year in succession, on both occasions as authors of a paper on cachectin. Another pairing in each of the two years was that of Mitsuya and Broder.

The number of authors per paper (Table 2) averaged at 5.7. This is down slightly from 1988's 6.0 for 1986 papers, although that figure was skewed by the 77 names attached to one paper on the genetic basis of Becker and Duchenne muscular dystrophy. With this anomaly removed, the 1986 average was 5.4. Incidentally, the names of three of those 77 authors appeared on the 1987 paper by M. Koenig and colleagues, Harvard Medical School, that described the cloning of Duchenne muscular dystrophy DNA.

Journals, Countries, and Institutions

As usual, *Nature* and *Science* account for about half of the papers (Table 3). In the case of *Science*, there has been a significant increase in the journal's "impact factor"—a measure of the degree to which papers in a particular journal are cited in the literature. While the rating for *Nature* has risen from 15.3 to 15.8, *Science*'s figure has gone up from 12.4 to 16.3. *Cell* and the *New England Journal of Medicine* remain in third and fourth places, respectively. But the *Journal of Experimental Medicine*, which appeared in fifth place in 1988 with four 1986 papers (all on tumor necrosis factor), has returned to a lower position with just two papers.

Table 3: The 22 journals that published the papers listed in the Bibliography. The numbers in parentheses are the 1988 impact factors for the journals. (The 1988 impact factor equals the number of 1988 citations received by the 1986-1987 articles in a journal divided by the number of articles published by the journal during that same period.) Data were taken from the 1988 *JCR®*. The figures at the right indicate how many papers from each journal appear in the Bibliography.

Journal	Number of Papers
Nature (15.8)	31
Science (16.3)	20
Cell (23.9)	13
N. Engl. J. Med. (21.1)	10
Proc. Nat. Acad. Sci. USA (10.0)	5
Annu. Rev. Biochem. (48.3)	3
JAMA—J. Am. Med. Assn. (5.3)	2
J. Biol. Chem. (6.5)	2
J. Exp. Med. (11.8)	2
Anal. Biochem. (2.4)	1
Annu. Rev. Immunol. (25.4)	1
Biochem. J. (3.9)	1
Ca—A Cancer J. Clin. (4.9)	1
DNA—J. Molec. Cell. Biol. (5.1)	1
J. Clin. Invest. (7.6)	1
Lab. Invest. (5.1)	1
Lancet (14.5)	1
Microbiol. Rev. (16.3)	1
Mol. Cell. Endocrinol. (2.9)	1
Nucl. Acid. Res. (4.3)	1
Prog. Neurobiol. (9.1)	1
Trends Biochem. Sci. (7.9)	1

One surprise is the performance of *Lancet*, which has only one paper in the listing, compared with four in 1988. In the past, *Lancet* has fared well in citation studies—for example, an analysis by Jean G. Shaw, Clinical Sciences Library, University of Leicester, UK, showed that in 1977 it had an impact factor of 8.6, compared with 2.6 for the *Journal of the American Medical Association* and 3.2 for the *British Medical Journal*.[15] As recorded in Table 3, the 1988 impact factor for *Lancet* was 14.5, not far behind the 15.8 scored by *Nature* and the 16.3 logged by *Science*. But the position of the *New England Journal of Medicine*

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	82	11	Canada, France, FRG, Italy, Japan, The Netherlands, UK
UK	11	4	Israel, Japan, US
France	7	1	FRG, Italy, US
Japan	7	3	UK, US
FRG	6	3	Australia, France, Italy, US
Australia	2	2	Belgium, FRG
The Netherlands	2	2	US
Belgium	1	1	Australia
Canada	1	1	US
Israel	1	1	UK
Italy	1	1	France, FRG, US
Mexico	1		

as the world's most influential medical journal remains clear. Its impact factor, reported as 12.5 for 1977 in the Shaw study, was 21.1 for 1988.

However, these journal impact data are complex and can be subjected to detailed analysis. Letters to the editor of *Lancet*, for example, achieve much greater impact than letters appearing in other journals.[16]

Table 4, which records countries for the various institutions represented in the listing, shows that, although the US remains strongly in the lead, its tally of national affiliations of papers has fallen significantly, from 94 out of 103 in 1988 to 82 out of 101 this year. Meanwhile, the UK share has risen sharply, from 6 to 11. This may come as a surprise to readers aware of the funding difficulties facing British science in recent times, but it is a reflection of the country's continuing strengths in the disciplines covered in the cited papers—neurobiology and molecular biology. France has also advanced from 4 to 7 papers, and Japan from 5 to 7.

Of the 108 unique institutions represented in the list, the most prolific (with 20 papers each to their credit) were Harvard (Medical School and University), the NIH, and the University of California (Los Angeles, Berkeley, San Diego, and San Francisco).

Conclusion

The listing of most-cited 1987 life-sciences papers gives little support to those who argue that citation analysis distorts the true character and topology of advancing science. Instead, it highlights what are known to be the major domains of research activity, while also encompassing specific papers that are having seminal influences in their fields. Repudiating claims that laboratory methods receive undue prominence in citation ratings, the 101 papers include only five (those by Piotr Chomczynski and Nicoletta Sacchi, NIH; Paul Matsudaira, MIT; Yusuke Nakamura *et al.*, University of Utah School of Medicine, Salt Lake City; Phillip A. Sharp, MIT; and Stanley Tabor and Charles C. Richardson, Harvard Medical School) that are specifically devoted to investigational techniques.

Yet these papers remind us that methods *are* of catalytic importance in science. The most highly cited is that by Tabor and Richardson (approximately 140 citations) on the polymerase chain reaction (PCR) that is now used to amplify tiny pieces of DNA. Last December *Science* selected DNA polymerase as its first "molecule of the year" in view of the tremendous value of PCR in disease diagnosis and other fields. In the second most highly cited methods paper (over 125 citations), Nakamura *et al.* described new genetic markers to help in mapping genes responsible for human diseases.

Finally, the high citation ratings achieved by papers on the genetic basis of Alzheimer's disease, CF, and manic-depressive illness place in true perspective the allegation that one way of making a substantial impact

in the scientific literature is to publish a demonstrably erroneous paper. Although the genes charted in these papers proved not to be those specifically responsible for the conditions in question, it would be naive to see such work as simply erroneous. Rather it represented in each case a step forward that helped to illuminate the problem, sharpen the tools of investigation, and narrow the range of solutions. Science is not, for the most part, an activity in which competing monkeys seek the "right" solution on a typewriter keyboard. It is, at heart, a social activity—and a process.

Note: ISI® regrets that in discussing 1988's compilation,[2] we stated that none of the most-cited 1986 papers came from authors working in Switzerland. In fact, the paper by Zlatko Dembic *et al.* (*Nature* 320:232-8, 1986) was written by researchers at the Basel Institute for Immunology, Switzerland.

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