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Current Comments®

EUGENE GARFIELD
INSTITUTE FOR SCIENTIFIC INFORMATION®
3501 MARKET ST., PHILADELPHIA, PA 19104

# The 1985 Nobel Prize in Medicine— Michael S. Brown and Joseph L. Goldstein Have Revolutionized Our Knowledge About Cholesterol Metabolism and Heart Disease

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Cholesterol has fascinated scientists since it was first isolated from gallstones in 1784. In fact it is perhaps the most highly decorated small molecule in biology. Thirteen Nobel Prizes have been awarded to scientists involved in cholesterol research. For instance, Heinrich O. Wieland (1927), Adolf O.R. Windaus (1928), Leopold Ružička (1939), Robert Robinson (1947), Otto P.H. Diels (1950), and John W. Cornforth (1975) were awarded the Nobel Prize in chemistry for work that led to determining the structure of cholesterol. Konrad E. Bloch and Feodor Lynen were awarded the 1964 Nobel Prize in physiology or medicine for defining the cholesterol biosynthetic pathway.[1]

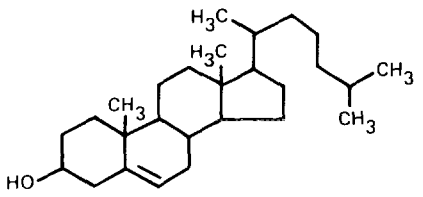
The 1985 Nobel Prize in physiology or medicine was also awarded for excellence in cholesterol research. Michael S. Brown and Joseph L. Goldstein, University of Texas Health Science Center, Dallas, were honored for their work in identifying the low-density lipoprotein receptor pathway—the mechanism controlling how the body's cells obtain cholesterol. In addition, they determined how an inherited defect in this pathway, occurring in the disease familial hypercholesterolemia, can lead to atherosclerosis, a disease resulting in cholesterol-clogged arteries. The Nobel Assembly of the Karolinska Institute in Stockholm stated that Brown and Goldstein have "revolutionized our knowledge about the regulation of cholesterol metabolism and the treatment of diseases caused by abnormally elevated cholesterol levels in the blood."[2] Understanding cholesterol metabolism is a key step in the development of various diet and drug therapies that will reduce dangerously high cholesterol levels in the bloodstream.

It is not surprising that cholesterol research has so often been recognized by awards. Present in all cells, cholesterol is of vital importance to the body. As an organic compound belonging to the steroid family (see Figure 1), it is a structural component in the cell membrane, which serves as a protective barrier between the cell and its environment. It is also the precursor in the synthesis of steroid hormones, vitamin D, and bile acids. The early history of cholesterol research is described by David Kritchevsky, associate director, Wistar Institute, Philadelphia, in one of the earliest books published on this topic.[3]

The body acquires cholesterol either by manufacturing it in the liver or by absorbing it from the fats found in food. For easier transport through the bloodstream, multicellular organisms attach a cholesterol molecule to a long-chain fatty acid by an ester linkage to make a cholesteryl ester. These cholesteryl esters are then packaged in a protective coating called lipoprotein.

There are four major classes of lipoproteins, as described by Donald S. Fredrickson, then at NIH and now president, Howard Hughes Medical Institute, Bethesda, Maryland: low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), intermediate-density lipo-

**Figure 1**: The molecular structure of cholesterol.




protein (IDL), and high-density lipoprotein (HDL).[4] These four classes were elucidated using an ultracentrifugal method developed in 1950 by John W. Gofman and colleagues, Division of Medical Physics, Donner Laboratory, University of California, Berkeley.[5]

LDL is the most abundant cholesterol-carrying lipoprotein in human plasma. It is a large spherical particle with a surface made of phospholipids arranged with their hydrophilic (water-loving) heads facing outside, allowing the LDL to be dissolved in the blood. Embedded in the LDL phospholipid surface is a large protein molecule, apoprotein B-100. Each LDL carries about 1,500 molecules of cholesteryl esters.

**Receptor Discovery**

When they first began working together in 1972, Brown and Goldstein questioned how cholesteryl esters are delivered to cells. Using tissue cultures of human skin cells, called fibroblasts, they found that these cells derive most of their cholesterol from LDL, suggesting that the fibroblasts contain highly specific receptors for LDL.

The key to understanding this receptor mechanism emerged from studies of cells from patients with familial hypercholesterolemia (FH), an inborn error of metabolism causing high levels of cholesterol in the blood. Transmitted as a dominant trait determined by a single gene pair (two alleles), FH exists in two different forms. Individuals with homozygous FH have inherited two mutant alleles, a problem affecting only one in a million children. These children have cholesterol levels six times higher than normal and develop severe atherosclerosis as early as the age of two. Individuals with heterozygous FH, a more common problem occurring in 1 out of 500 persons, have inherited one mutant allele and one normal allele. They often develop clogged arteries and experience heart attacks by their early thirties.[6]

Brown and Goldstein confirmed the existence of an LDL receptor by incubating both normal and homozygous FH fibroblasts with LDL tagged with radioactive iodine. These studies established that normal cells have high-affinity binding sites for LDL, while other homozygous FH cells lacked these high-affinity receptors.

Brown and Goldstein published their findings in a landmark 1974 paper, the first to identify the LDL receptor. As shown in Table 1, which lists Brown and Goldstein's most-cited papers in descending order by citation count, this is their third most-cited paper. Throughout this essay, we will reference various papers in Table 1 by giving a notation in parentheses that specifies the table number and paper number. In this case, Table 1-3 refers to the third paper listed in Table 1.

This 1974 paper is one of five core papers for the 1985 research front on "Characterization of LDL and HDL and their effects on cholesterol metabolism" (#85-2566). Table 2 lists the research fronts with core and citing papers by Brown and Goldstein.

Finding the LDL receptor was a major breakthrough in cholesterol research. Arno G. Motulsky, director, Center for Inherited Diseases, University of Washington, Seattle, recalls that "scientists working on lipoprotein physiology and pathology had a new paradigm, and all research in this area had to pay attention to these findings."[7] Motulsky was head of the laboratory in which Goldstein did early blood lipid-level research.

**Cholesterol Pathway**

Discovery of the LDL receptor was the first step in learning how cholesterol travels into a cell. In a series of studies, Brown and Goldstein were able to show that after the LDL binds to a receptor, it is internalized by the cell as an LDL-receptor complex. In 1976, in collaboration with Richard G.W. Anderson, also of the University of Texas Health Science Center, they established that the internalization of the LDL-receptor complex occurs via receptor-mediated endocytosis, a process in which the surface membrane pouches inward and pinches off to form vesicles (Table 1-10). In a paper published in *Nature* in 1979, Goldstein, Anderson, and Brown reviewed some of the experiments delineating the endocytotic process. Cited over 1,000 times, this Citation Classic is Brown and Goldstein's most-cited paper (Table 1-1). It is also the central core paper for the research front on "Receptor-mediated endocytosis and effects of influenza and other viruses on cell proteins" (#85-1920). The immediacy of this field is apparent in that over 80 percent of the 46 core papers for this front were published since 1980. About 70 papers were published on this topic in 1985.

Brown and Goldstein then ascertained that once the LDL-receptor complex enters the cell, lysosomes (cell components containing digestive enzymes) break down the LDL protective coating, releasing the cholesterol inside the cell.[8] The amount of cholesterol released into the cell interior controls the cell's cholesterol metabolism by modulating three processes. First, an accumulation of cholesterol reduces the cell's ability to make its own cholesterol by suppressing 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase)—the rate-determining enzyme of cholesterol biosynthesis. This suppression causes the cell to be dependent on external cholesterol from the receptor-mediated uptake of LDL (Table 1-21). Second, the cholesterol activates the enzyme cholesterol acyltransferase to promote the storage of cholesterol in the cell (Table 1-15).

The third and most significant process regulated by the accumulation of cholesterol in the cell is a negative-feedback mechanism resulting in the suppression of LDL-receptor synthesis. This action allows cells to adjust the number of LDL receptors to meet their varying demands for cholesterol without causing overload (Table 1-18). For example, when fibroblasts are actively dividing, requiring cholesterol to synthesize new membrane material, they maintain a maximum number of LDL receptors. But in cells that are not proliferating, the incoming cholesterol begins to accumulate, causing the cells to stop making LDL receptors.

In their second most-quoted paper, published in the 1977 *Annual Review of Biochemistry*, Brown and Goldstein reviewed their numerous findings and concluded that patients with FH have cells incapable of making a proper amount of LDL receptors (Table 1-2). These patients cannot bind, internalize, and degrade cholesterol-containing LDL efficiently. Therefore, cholesterol builds up in the bloodstream, which may cause it to accumulate in the arterial walls, leading to the risk of heart attacks. Cited over 1,000 times, this article was one of the most-referenced life-sciences articles between 1977 and 1979.[9] It is 1 of 14 core papers on "LDL metabolism and effects of cholesterol on lipoprotein receptors in humans" (#85-1921). This paper is included in Figure 2, a chronological distribution of citations to Brown and Goldstein's three most-cited papers. A similar analysis of the hundreds of articles in our annual studies of most-cited papers might demonstrate the value of such data in forecasting future research activity.

**Implications**

Elucidation of the LDL-receptor pathway and the receptor deficiency found in

**Table 1**: Papers coauthored by Brown and Goldstein and cited in the *SCI®* from 1955 to 1985. The papers are arranged in descending order, according to number of citations. A = total number of citations. B = bibliographic citation. *SCI/SSCI®* research fronts to which the paper is core are listed in parentheses after the bibliographic citation.

| | A | B |
|---|---|---|
| 1. | 1091 | **Goldstein J L, Anderson R G W & Brown M S.** Coated pits, coated vesicles, and receptor-mediated endocytosis. *Nature* 279:679-85, 1979. (83-0016, 84-2014, 85-1920) |
| 2. | 1052 | **Goldstein J L & Brown M S.** The low-density lipoprotein pathway and its relation to atherosclerosis. *Annu. Rev. Biochem.* 46:897-930, 1977. (78-0737, 83-0053, 84-6695, 85-1921) |
| 3. | 649 | **Goldstein J L & Brown M S.** Binding and degradation of low density lipoproteins by cultured human fibroblasts. *J. Biol. Chem.* 249:5153-62, 1974. (75-0386, 76-0351, 77-0225, 78-0737, 79-0395, 80-0539, 81-0142, 82-1023, 83-0053, 84-6695, 85-2566) |
| 4. | 567 | **Brown M S & Goldstein J L.** Receptor-mediated control of cholesterol metabolism. *Science* 191:150-4, 1976. (76-0351, 77-0225, 83-0053) |
| 5. | 350 | **Goldstein J L, Basu S K, Brunschede G Y & Brown M S.** Release of low density lipoprotein from its cell surface receptor by sulfated glycosaminoglycans. *Cell* 7:85-95, 1976. (77-0225, 79-0395, 80-0539, 81-0142, 82-1023, 83-0053, 84-6695, 85-2566) |
| 6. | 342 | **Brown M S, Dana S E & Goldstein J L.** Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in cultured human fibroblasts. *J. Biol. Chem.* 249:789-96, 1974. (75-0386, 76-0351, 77-0225, 78-0737, 79-0395, 80-0539, 81-1029) |
| 7. | 332 | **Anderson R G W, Brown M S & Goldstein J L.** Role of the coated endocytic vesicle in the uptake of receptor-bound low density lipoprotein in human fibroblasts. *Cell* 10:351-64, 1977. (78-0172, 79-0171, 81-0106, 82-0125, 83-0860) |
| 8. | 326 | **Brown M S & Goldstein J L.** Familial hypercholesterolemia: defective binding of lipoproteins to cultured fibroblasts associated with impaired regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. *Proc. Nat. Acad. Sci. USA* 71:788-92, 1974. (75-0386, 76-0351, 77-0225, 78-0737, 79-0395, 85-3356) |
| 9. | 321 | **Brown M S, Kovanen P T & Goldstein J L.** Regulation of plasma cholesterol by lipoprotein receptors. *Science* 212:628-35, 1981. (83-0053, 85-1921) |
| 10. | 252 | **Anderson R G W, Goldstein J L & Brown M S.** Localization of low density lipoprotein receptors on plasma membrane of normal human fibroblasts and their absence in cells form a familial hypercholesterolemia homozygote. *Proc. Nat. Acad. Sci. USA* 73:2434-8, 1976. (77-0225) |
| 11. | 243 | **Brown M S, Dana S E & Goldstein J L.** Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in human fibroblasts by lipoproteins. *Proc. Nat. Acad. Sci. USA* 70:2162-6, 1973. (75-0386, 76-0351, 78-0739, 81-1029) |
| 12. | 241 | **Brown M S, Faust J R & Goldstein J L.** Role of the low density lipoprotein receptor in regulating the content of free and esterified cholesterol in human fibroblasts. *J. Clin. Invest.* 55:783-93, 1975. (76-0351, 77-0225, 79-0395, 81-1029) |
| 13. | 230 | **Goldstein J L, Ho Y K, Basu S K & Brown M S.** Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. *Proc. Nat. Acad. Sci. USA* 76:333-7, 1979. (81-1604, 82-0496, 85-1921) |
| 14. | 215 | **Brown M S & Goldstein J L.** Suppression of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and inhibition of growth of human fibroblasts by 7-Ketocholesterol. *J. Biol. Chem.* 249:7306-14, 1974. (76-0351, 77-0778, 78-0738, 79-0395, 80-0756, 81-1029) |
| 15. | 209 | **Goldstein J L, Dana S E & Brown M S.** Esterification of low density lipoprotein cholesterol in human fibroblasts and its absence in homozygous familial hypercholesterolemia. *Proc. Nat. Acad. Sci. USA* 71:4288-92, 1974. (76-0351, 77-0225, 78-0737, 79-0395, 81-1029, 82-1023) |
| 16. | 206 | **Brown M S, Anderson R G W & Goldstein J L.** Recycling receptors: the round-trip itinerary of migrant membrane proteins. *Cell* 32:663-7, 1983. (84-2014, 85-1920) |
| 17. | 202 | **Basu S K, Goldstein J L, Anderson R G W & Brown M S.** Monensin interrupts the recycling of low density lipoprotein receptors in human fibroblasts. *Cell* 24:493-502, 1981. (83-0860, 84-2014) |
| 18. | 186 | **Brown M S & Goldstein J L.** Regulation of the activity of the low density lipoprotein receptor in human fibroblasts. *Cell* 6:307-16, 1975. (77-0225, 82-1023) |
| 19. | 182 | **Brown M S & Goldstein J L.** Multivalent feedback regulation of HMG CoA reductase, a control mechanism coordinating isoprenoid synthesis and cell growth. *J. Lipid Res.* 21:505-17, 1980. (82-0360, 84-0467, 85-0429) |
| 20. | 173 | **Goldstein J L & Brown M S.** Familial hypercholesterolemia: identification of a defect in the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity associated with overproduction of cholesterol. *Proc. Nat. Acad. Sci. USA* 70:2804-8, 1973. (75-0386, 76-0351, 77-0225) |
| 21. | 171 | **Ho Y K, Brown M S, Bilheimer D W & Goldstein J L.** Regulation of low density lipoprotein receptor activity in freshly isolated human lymphocytes. *J. Clin. Invest.* 58:1465-74, 1976. (77-0225, 82-1023) |

22. 167 **Bilheimer D W, Goldstein J L, Grundy S M & Brown M S.** Reduction in cholesterol and low density lipoprotein synthesis after portacaval shunt surgery in a patient with homozygous familial hypercholesterolemia. *J. Clin. Invest.* 56:1420-30, 1975. (77-0225)

23. 151 **Goldstein J L, Dana S E, Brunschede G Y & Brown M S.** Genetic heterogeneity in familial hypercholesterolemia: evidence for two different mutations affecting functions of low-density lipoprotein receptor. *Proc. Nat. Acad. Sci. USA* 72:1092-6, 1975. (76-0351, 77-0225)

24. 149 **Brown M S, Faust J R, Goldstein J L, Kaneko I & Endo A.** Induction of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in human fibroblasts incubated with compactin (ML-236B), a competitive inhibitor of the reductase. *J. Biol. Chem.* 253:1121-8, 1978. (80-0757, 81-1029, 82-0360)

25. 147 **Brown M S, Dana S E & Goldstein J L.** Cholesterol ester formation in cultured human fibroblasts: stimulation by oxygenated sterols. *J. Biol. Chem.* 250:4025-7, 1975. (81-1029)

26. 146 **Faust J R, Goldstein J L & Brown M S.** Receptor-mediated uptake of low density lipoprotein and utilization of its cholesterol for steroid synthesis in cultured mouse adrenal cells. *J. Biol. Chem.* 252:4861-71, 1977. (81-0129, 82-0494)

27. 140 **Basu S K, Goldstein J L, Anderson R G W & Brown M S.** Degradation of cationized low density lipoprotein and regulation of cholesterol metabolism in homozygous familial hypercholesterolemia fibroblasts. *Proc. Nat. Acad. Sci. USA* 73:3178-82, 1976. (79-0395, 82-0496, 85-1921)

28. 140 **Goldstein J L, Dana S E, Faust J R, Beaudet A L & Brown M S.** Role of lysosomal acid lipase in the metabolism of plasma low density lipoprotein. *J. Biol. Chem.* 250:8487-95, 1975. (76-0351, 77-0225)

29. 138 **Brown M S & Goldstein J L.** Familial hypercholesterolemia: a genetic defect in the low-density lipoprotein receptor. *N. Engl. J. Med.* 294:1386-90, 1976. (77-0225)

30. 137 **Brown M S, Kovanen P T & Goldstein J L.** Receptor-mediated uptake of lipoprotein-cholesterol and its utilization for steroid synthesis in the adrenal cortex. *Recent Prog. Hormone Res.* 35:215-57, 1979. (81-0129, 82-0494, 83-0053)

31. 134 **Kovanen P T, Bilheimer D W, Goldstein J L, Jaramillo J J & Brown M S.** Regulatory role for hepatic low density lipoprotein receptors *in vivo* in the dog. *Proc. Nat. Acad. Sci. USA* 78:1194-8, 1981. (84-0467)

32. 129 **Brown M S, Goldstein J L & Dietschy J M.** Active and inactive forms of 3-hydroxy-3-methylglutaryl coenzyme A reductase in the liver of the rat. *J. Biol. Chem.* 254:5144-9, 1979. (80-0436, 81-0768, 82-0360)

33. 119 **Brown M S, Dana S E & Goldstein J L.** Receptor-dependent hydrolysis of cholesteryl esters contained in plasma low density lipoprotein. *Proc. Nat. Acad. Sci. USA* 72:2925-9, 1975. (76-0351, 77-0225)

34. 116 **Goldstein J L & Brown M S.** Lipoprotein receptors, cholesterol metabolism, and atherosclerosis. *Arch. Pathol. Lab. Med.* 99:181-4, 1975. (76-0351, 77-0225)

35. 115 **Brown M S & Goldstein J L.** Expression of the familial hypercholesterolemia gene in heterozygotes: mechanism for a dominant disorder in man. *Science* 185:61-3, 1974. (75-0386, 76-0351)

36. 114 **Havel R J, Goldstein J L & Brown M S.** Lipoproteins and lipid transport. (Bondy P K & Rosenberg L E, eds.) *Metabolic control and disease.* Philadelphia: Saunders, 1980. p. 393-494. (85-3356)

37. 111 **Kovanen P T, Faust J R, Brown M S & Goldstein J L.** Low density lipoprotein receptors in bovine adrenal cortex. I. Receptor-mediated uptake of low density lipoprotein and utilization of its cholesterol for steroid synthesis in cultured adrenocortical cells. *Endocrinology* 104:599-609, 1979. (81-0129, 82-0494)

38. 108 **Goldstein J L, Ho Y K, Brown M S, Innerarity T L & Mahley R W.** Cholesteryl ester accumulation in macrophages resulting from receptor-mediated uptake and degradation of hypercholesterolemic canine $\beta$-very low density lipoproteins. *J. Biol. Chem.* 255:1839-48, 1980. (81-1604, 82-0496)

39. 96 **Brown M S, Basu S K, Falck J R, Ho Y K & Goldstein J L.** The scavenger cell pathway for lipoprotein degradation: specificity of the binding site that mediates the uptake of negatively-charged LDL by macrophages. *J. Supramolec. Struct.* 13:67-81, 1980. (82-0496)

40. 90 **Brown M S, Ho Y K & Goldstein J L.** The cholesteryl ester cycle in macrophage foam cells. *J. Biol. Chem.* 255:9344-52, 1980. (82-0496)

41. 88 **Goldstein J L & Brown M S.** Familial hypercholesterolemia: a genetic regulatory defect in cholesterol metabolism. *Amer. J. Med.* 58:147-50, 1975. (76-0351)

42. 82 **Goldstein J L, Helgeson J A S & Brown M S.** Inhibition of cholesterol synthesis with compactin renders growth of cultured cells dependent on the low density lipoprotein receptor. *J. Biol. Chem.* 254:5403-9, 1979. (81-1029)

43. 80 **Brown M S & Goldstein J L.** Lipoprotein metabolism in the macrophage: implications for cholesterol deposition in atherosclerosis. *Annu. Rev. Biochem.* 52:223-61, 1983. (85-1921)

| A | | B |
|---|---|---|
| 44. | 75 | **Brown M S, Brunschede G Y & Goldstein J L.** Inactivation of 3-hydroxy-3-methylglutaryl coenzyme A reductase *in vitro*. *J. Biol. Chem.* 250:2502-9, 1975. (77-0225) |
| 45. | 70 | **Goldstein J L & Brown M S.** Familial hypercholesterolemia. (Stanbury J B, Wyngaarden J B, Fredrickson D S, Goldstein J L & Brown M S, eds.) *The metabolic basis of inherited disease.* New York: McGraw-Hill, 1983. p. 672-712. (84-0467, 85-3356) |
| 46. | 70 | **Ho Y K, Brown M S & Goldstein J L.** Hydrolysis and excretion of cytoplasmic cholesteryl esters by macrophages: stimulation by high density lipoprotein and other agents. *J. Lipid Res.* 21:391-8, 1980. (82-0496) |
| 47. | 48 | **Bilheimer D W, Grundy S M, Brown M S & Goldstein J L.** Mevinolin and colestipol stimulate receptor-mediated clearance of low density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. *Proc. Nat. Acad. Sci. USA* 80:4124-8, 1983. (85-1921) |
| 48. | 30 | **Goldstein J L, Kita T & Brown M S.** Defective lipoprotein receptors and atherosclerosis. *N. Engl. J. Med.* 309:288-95, 1983. (84-0467, 85-1921) |
| 49. | 27 | **Goldstein J L & Brown M S.** Lipoprotein receptors: genetic defense against atherosclerosis. *Clin. Res.* 30:417-26, 1982. (84-0467) |


**Table 2**: 1985 *SCI®/SSCI®* research fronts on lipoproteins and cholesterol metabolism in which Brown and/or Goldstein are core authors. A = number. The first two numbers indicate the year of the research front. B = name. C = number of core items. Number in parentheses indicates the number of core papers written by Brown and/or Goldstein. D = number of citing items for the year indicated.

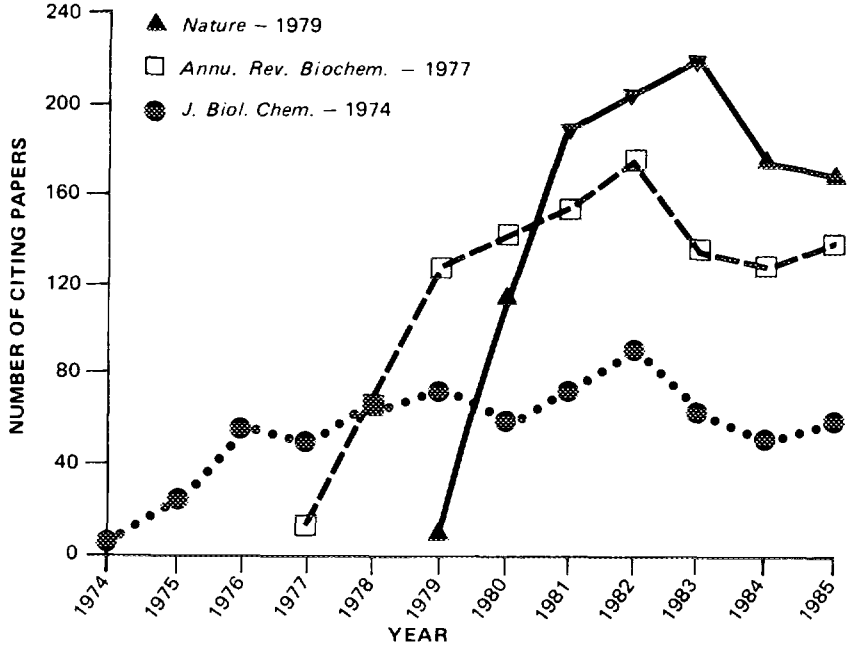
| A | B | C | D |
|---|---|---|---|
| 85-0429 | Regulation of cholesterol synthesis and 3-hydroxy-3-methylglutaryl coenzyme-A reductase in rat liver and other cells | 8 (1) | 162 |
| 85-1920 | Receptor-mediated endocytosis and effects of influenza and other viruses on cell proteins | 46 (2) | 929 |
| 85-1921 | LDL metabolism and effects of cholesterol on lipoprotein receptors in humans | 14 (7) | 392 |
| 85-2566 | Characterization of LDL and HDL and their effects on cholesterol metabolism | 5 (2) | 426 |
| 85-3166 | Metabolism and pathology of human apolipoproteins and LDL | 6 (1) | 164 |
| 85-3356 | Cholesterol levels and LDL-receptor activity in patients with familial hypercholesterolemia | 5 (3) | 99 |

patients with FH has opened new research routes for treatment of cholesterol-related heart diseases. For instance, new drugs such as compactin and mevinolin have been developed to inhibit cholesterol biosynthesis. These drugs make it possible to stimulate the one normal allele in patients with heterozygous FH, thereby doubling the number of LDL receptors synthesized by that allele. This provides the patient with a normal complement of functional LDL receptors.[10]

Patients with homozygous FH require a more direct therapeutic approach. In 1983 a team of surgeons led by Thomas E. Starzl, Department of Surgery, University of Pittsburgh Health Center, in collaboration with Brown and Goldstein, performed a combination liver-heart transplant on a six-year-old girl with homozygous FH. With its large size and numerous LDL receptors, the liver metabolizes more cholesterol than any other organ. The liver transplant was designed to provide a new source of LDL receptors. The heart transplant was necessary to replace an organ already damaged by atherosclerosis. The operation was successful in reducing the girl's abnormally high cholesterol level.[11]

While FH is a dangerous disease, it accounts for only 5 percent of the heart attacks in patients under the age of 60. The work of Brown and Goldstein, however, has important implications for the other 95 percent of the general population suffering from heart problems not caused by FH. Cholesterol-related heart problems may be caused by the prevalence in Western industrialized populations of dangerously high blood levels of LDL. Many studies point to a general association of high blood cholesterol levels with heart attacks, including the seven-country study conducted by Ancel Keys,

**Figure 2**: Chronological distribution of citations to Brown and Goldstein's three most-cited papers listed in Table 1.




University of Minnesota School of Public Health, Minneapolis.[12]

Brown and Goldstein propose that diet and heredity may be two major reasons for the higher blood levels of LDL found in Western populations. The high-fat, high-cholesterol Western diet may suppress the manufacture of LDL receptors, thereby raising bloodstream cholesterol to levels that cannot be adequately disposed of by existing LDL receptors. When even moderate amounts of animal fat are ingested, the LDL level rises significantly. But this level is different in each person, suggesting that genetic factors play a role.[1]

## Biographies

Michael S. Brown was born in 1941 in New York City. He obtained his undergraduate and medical education at the University of Pennsylvania, Philadelphia, receiving his medical degree in 1966. While in medical school, Brown studied the effect of immobilization on the propulsive activity of the small intestine.[13]

Joseph L. Goldstein was born in 1940 in Sumter, South Carolina, and received his undergraduate degree from Washington and Lee University, Lexington, Virginia, a small, private institution. He obtained his medical degree from the University of Texas Southwestern Medical School, Dallas, in 1966. As a medical student, he became interested in the excretion mechanisms of hepatic sulfobromophthalein sodium in the blood of newborn and premature infants.[14]

Brown and Goldstein first met as residents in 1966 at the Massachusetts General Hospital, Boston. In 1968 they both went to NIH to work as clinical associates. Brown worked in the Laboratory of Biochemistry, under Earl R. Stadtman, studying the regulation of the enzyme glutamine synthetase.[15] Goldstein worked under 1968 Nobelist Marshall W. Nirenberg, studying the molecular biology of peptide-chain termination in

the Laboratory of Biochemical Genetics.[16]

In 1971 Brown joined the faculty of the University of Texas Health Science Center, Dallas, while Goldstein spent two years at the University of Washington School of Medicine, Seattle, in the laboratory of Arno G. Motulsky, mentioned earlier. It was during this time that Goldstein began to study the genetics of elevated levels of lipids in the blood. Three papers resulting from this work appeared in the same issue of the *Journal of Clinical Investigation*. Two of these were each cited over 300 times.[17,18]

Goldstein then followed Brown to the University of Texas to head the Division of Medical Genetics in 1972. Today Brown is the director of the Center for Genetic Disease, while Goldstein is chairman of the Department of Molecular Genetics. Both are professors of medicine as well.

Their remarkable work has made Brown and Goldstein the corecipients of other prestigious awards. In 1985 alone, they received the Albert D. Lasker Award in Basic Medical Research, the American Society of Human Genetics William Allan Award, and the 3M Award from the Federation of American Societies for Experimental Biology. In 1984 they received the Louisa Gross Horowitz Award for their work in biochemistry. In 1983 Brown and Goldstein were mentioned in our essay on the awards of science as winners of the 1982 Lita Annenberg Hazen Award for Excellence in Clinical Research.[19]

**Research-Front Data**

Brown and Goldstein's research has made a significant impact since their

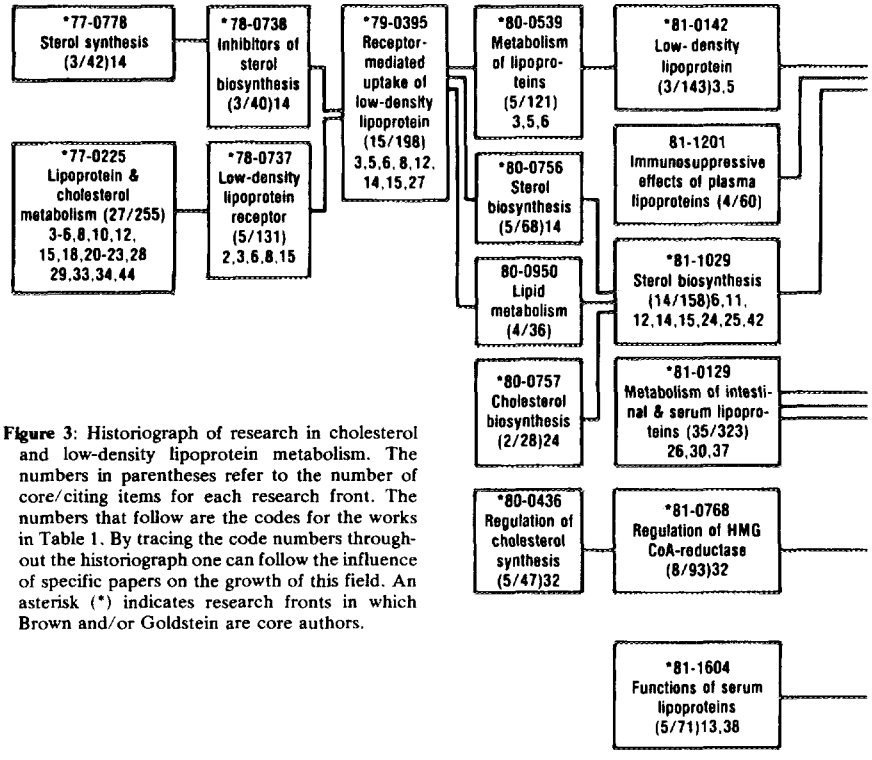



**Figure 3**: Historiograph of research in cholesterol and low-density lipoprotein metabolism. The numbers in parentheses refer to the number of core/citing items for each research front. The numbers that follow are the codes for the works in Table 1. By tracing the code numbers throughout the historiograph one can follow the influence of specific papers on the growth of this field. An asterisk (*) indicates research fronts in which Brown and/or Goldstein are core authors.

first joint paper was published in 1973 (Table 1-11). Both rank among the 1,000 scientists most cited between 1965 and 1978.[20] Since only 5 years of this 14-year study include their joint work, their citation count is all the more impressive. Had we limited this study to the period of 1974 to 1978, about two-thirds of the authors would drop from the list.

It is interesting to note that of the more than 200 papers Brown and Goldstein have published together, about 50 percent have been cited less than 25 times. This type of citation distribution seems to be a universal characteristic of prolific authors. Some of the earlier work is superseded by later papers or incorporated into review papers. I have discussed this topic in more detail in an earlier essay.[21]

Figure 3 is a historiograph showing the development and progress of their work from 1977 to 1985 as reflected in citation analysis. Each box includes the research-front name, the number of core articles, and the number of citing papers. The linkage of the annual fronts that are included here is determined by the continuity of the core literature from year to year. If the same core publications are cited at the required thresholds in two adjacent years, a string is established. Each box also contains numbers following the core and citing numbers. These correspond to the papers by Brown and Goldstein found in Table 1.

Figure 4 is a second-level (C2) multidimensional-scaling map for the research front on "Lipoprotein metabolism and circulatory disorders" (#85-0512). The map shows how related lower level (C1) fronts are linked by co-citation. This map includes fronts #85-2566 and #85-1921, mentioned earlier as contain-

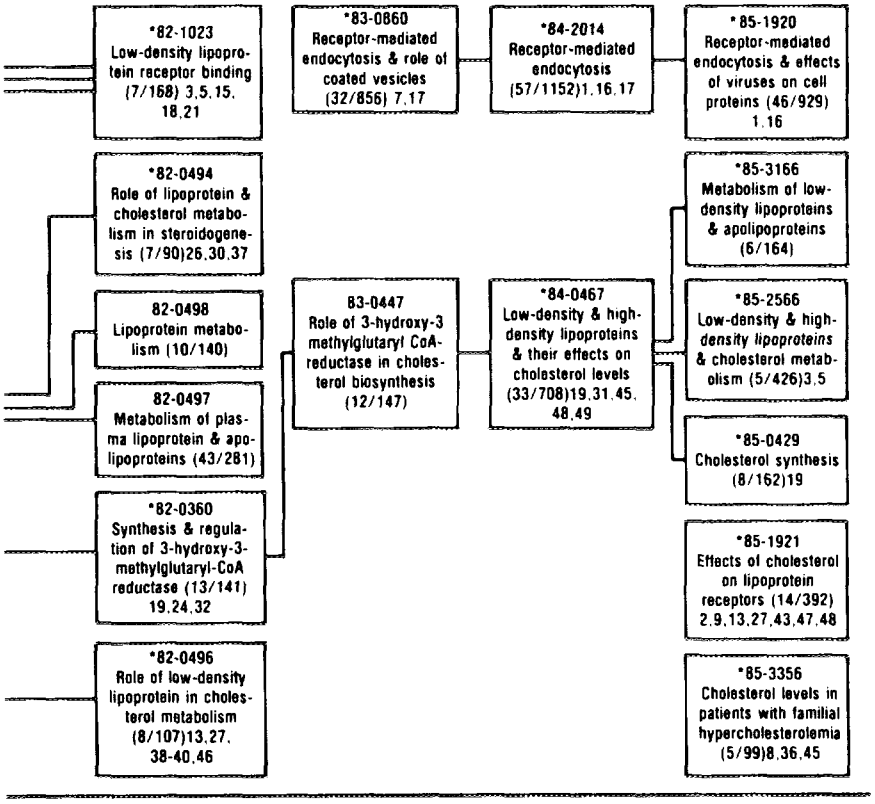
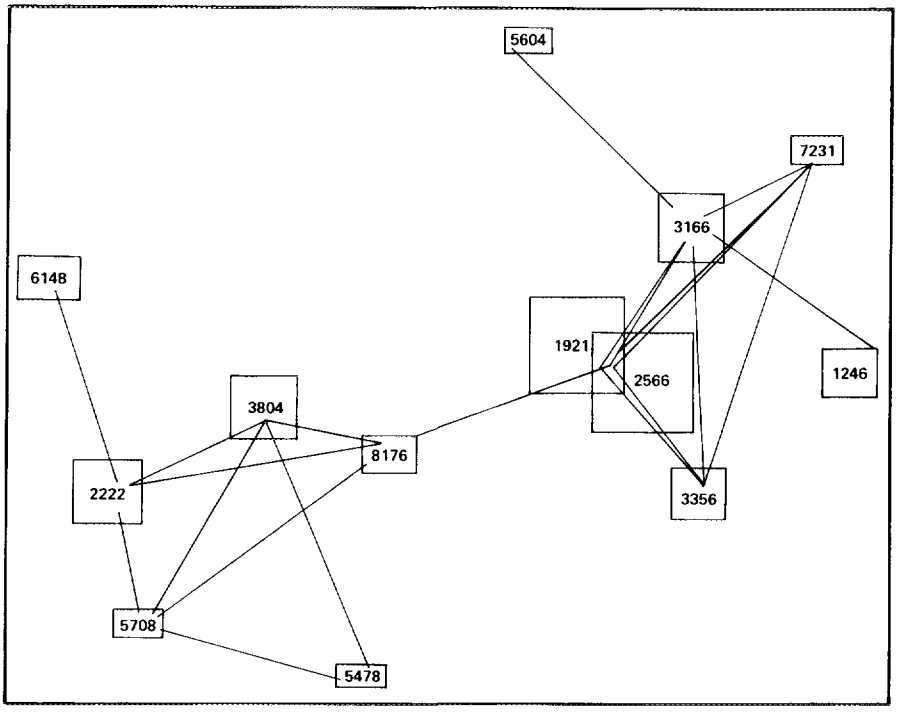


**Figure 4**: Multidimensional-scaling map for C2-level research front #85-0512, "Lipoprotein metabolism and circulatory disorders," showing links between C1-level research fronts. A = 1985 research-front number. B = name. The number of core/citing items is in parentheses. The size of the box around the number on the map indicates the relative size of the citing literature.




**KEY**

| A | B |
|---|---|
| 85-1246 | Effects of triglycerides on activity of lipoprotein lipase in human and rat adipose tissue and serum (4/90) |
| 85-1921 | LDL metabolism and effects of cholesterol on lipoprotein receptors in humans (14/392) |
| 85-2222 | Role of endothelial injury, vascular smooth-muscle cells, and platelet-derived growth factor in pathogenesis of atherosclerosis (3/159) |
| 85-2566 | Characterization of LDL and HDL and their effects on cholesterol metabolism (5/426) |
| 85-3166 | Metabolism and pathology of human apolipoproteins and LDL (6/164) |
| 85-3356 | Cholesterol levels and LDL-receptor activity in patients with familial hypercholesterolemia (5/99) |
| 85-3804 | Vascular smooth muscle in cell culture (5/168) |
| 85-5478 | Endothelial injury, arterial lesion formation, and vascular grafts in rats (3/39) |
| 85-5604 | Lipoprotein metabolism and the role of LDL and apolipoprotein-E in hyperlipoproteinemia and other disorders (3/45) |
| 85-5708 | Studies of biochemical and genetic causal agents of atherosclerosis and other circulatory diseases (3/48) |
| 85-6148 | Effect of platelet-derived growth factor on cell activation, cell proliferation, and chemotaxis (2/77) |
| 85-7231 | Metabolism of apolipoproteins and LDL in rat and human liver (3/49) |
| 85-8176 | Human and rat arterial smooth-muscle cells in primary culture and endothelial lesions of atherosclerosis (2/64) |

ing key core papers by Brown and Goldstein.

## Conclusion

Brown and Goldstein's work is an excellent example of the multidisciplinary synthesis of medicine and basic science research. Both are scientists specializing in internal medicine who continue to work as academic scientists. The success of Brown and Goldstein demonstrates the strength and viability of clinical investigation. Motulsky notes that their collaboration is successful because their talents are complementary. He states that "the creative synthesis of concepts and methods from diverse fields such as genetics, medicine, cell biology, molecular biology, biochemistry, pathology, pharmacology, electron microscopy, nuclear medicine, immunology, and surgery, which they have applied in their work, is distinctly unusual in this age of specialization."[7]

* * * * *

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