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Presentation of the Kober Medal

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AAP Kober Medal

This is the first time in its 77-year history that the Kober medal has been given to two individuals. Sharing of the medal on this occasion is appropriate because the partnership of Michael S. Brown and Joseph L. Goldstein has created a new paradigm for biomedical research. In her book Creative Collaboration, Vera John-Steiner points out that most successful scientific partnerships, such as that of Brown and Goldstein, involve the complementarity of equals (1). This type of collaboration is effective because any individual, no matter how gifted, can realize only a subset of human potential, and partnerships broaden, refine, change, and expand individual possibilities. It is for this reason that great ideas emerge more commonly from the exchange of ideas than from solitary introspection. Scientific collaborations have common features that include equal sharing of recognition and rewards, joint authorship of all publications, absolute trust, confidence in the other's abilities, certainty that disagreements can be resolved, and playing different roles in the partnership (1). In addition, virtually all scientific collaborations since that of Pierre and Marie Curie involve one person John-Steiner terms a "thinker-dreamer" and another a "thinker-doer" (1). One should not overdo this analogy in the present instance (Mike and Joe sometimes switch roles), but in fact all of these features characterize the remarkable and continuing partnership of Brown and […]

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Presentation of the Kober Medal to Joseph L. Goldstein and Michael S. Brown

Daniel W. Foster and Jean D. Wilson

This is the first time in its 77-year history that the Kober medal has been given to two individuals. Sharing of the medal on this occasion is appropriate because the partnership of Michael S. Brown and Joseph L. Goldstein has created a new paradigm for biomedical research. In her book *Creative Collaboration*, Vera John-Steiner points out that most successful scientific partnerships, such as that of Brown and Goldstein, involve the complementarity of equals (1). This type of collaboration is effective because any individual, no matter how gifted, can realize only a subset of human potential, and partnerships broaden, refine, change, and expand individual possibilities. It is for this reason that great ideas emerge more commonly from the exchange of ideas than from solitary introspection. Scientific collaborations have common features that include equal sharing of recognition and rewards, joint authorship of all publications, absolute trust, confidence in the other's abilities, certainty that disagreements can be resolved, and playing different roles in the partnership (1). In addition, virtually all scientific collaborations since that of Pierre and Marie Curie involve one person John-Steiner terms a "thinker-dreamer" and another a "thinker-doer" (1). One should not overdo this analogy in the present instance (Mike and Joe sometimes switch roles), but in fact all of these features characterize the remarkable and continuing partnership of Brown and Goldstein. Creation of a successful collaboration — requiring some transcending of individuality — is itself a creative act, and consequently it is appropriate that we honor Mike and Joe as individuals and at the same time acclaim their remarkable thirty-year collaboration that began as a friendship in Boston and Bethesda and came to fulfillment in Dallas.

The protagonists

Joe Goldstein grew up in Kingstree, South Carolina, which was named after a battle of the Revolutionary War but is now famous as his birthplace (Figure 1). His parents, Frances Alpert and Isadore E. Goldstein, were merchants. Joe began life as a gunslinger, but in high school his interest shifted to journalism (Figure 1). He was editor of the school newspaper (*The Boll Weevil*) and the yearbook. He was president of his class and of the student body and class valedictorian. Joe attended Washington and Lee University, where he majored in chemistry and biology and was again class valedictorian. His decision to become a physician was influenced by a high school chemistry teacher and by a cousin who was an internist, and in 1962 he came to the University of Texas Southwestern Medical School because fraternity brothers from Dallas convinced him that the school was up and coming. Joe hit the school like a cyclone and impressed the faculty and the student body as an intellectual dynamo, unlike any other student that most of us had ever encountered. To wit, he won the Ho Din Award as outstanding member of the class of 1966 (Figure 1).

He was introduced to research as a student fellow in the laboratory of Burton Combes, where he developed a new spectrophotometric assay for measuring conjugated forms of bromsulfothalein (BSP) and used this technique to investigate the regulation of BSP metabolism in the liver (2–5). This first taste of discovery proved fatal to his original plan to be a neurosurgeon, and by the time he was a fourth-year student, he had worked out a plan with Dr. Donald Seldin to pursue a training program consisting of a medical residency, research training, and a fellowship in medical genetics in preparation for returning to Southwestern to head a division of medical genetics in the Department of Internal Medicine. It was common in those days to make such arrangements with house staff officers but highly unusual to make a faculty commitment to a medical student. At any rate, when Joe left medical school he knew he had a job.

From 1966 to 1968 he was a medicine resident at the Massachusetts General Hospital (Figure 2). This MGH house staff photograph from 1968 contains an impressive number of future academicians (including six additional future members of the AAP), and it was here that Joe became acquainted with Mike Brown.

In 1968 Joe became a Clinical Associate in the National Heart Institute and worked with Tom Caskey in Marshall Nirenberg's laboratory, where, in studying the mechanism of protein synthesis, he characterized a new GTP-binding protein that stimulates release

Figure 1
Joe Goldstein, a native of Kingstree, South Carolina, shown as a young gunslinger, as editor of his high school newspaper, *The Boll Weevil*, and receiving the Ho Din Award as outstanding member of the UT Southwestern Medical School class of 1966.

Figure 2
The medical house staff at the Massachusetts General Hospital in 1968. In addition to Joe Goldstein (white arrow), Mike Brown (black arrow), Daniel Federman, and Alexander Leaf (the front row), the group includes six other future members of the AAP (David W. Bilheimer, David C. Dale, John D. Minna, Suzanne Oparil, Thomas P. Stossel, and Richard M. Weinshilboum).

of polypeptide chains following termination of synthesis (6). In keeping with the Seldin plan, Joe spent 1970–1972 as a fellow in medical genetics at the University of Washington. With Arno Motulsky he described the syndrome of combined hyperlipidemia, the most common monogenic cause of myocardial infarction (7), and he learned the techniques of tissue culture from Stanley Gartler (8). In 1972 Joe returned to Dallas to set up a division of medical genetics in the Department of Internal Medicine. At the beginning he had two grants — one from the NIH to study the hormonal regulation of phosphoprotein synthesis and one from the American Heart Association to study familial hypercholesterolemia.

Figure 3
Joe Goldstein's collection of art is rich in glass and graphics.

No description of Joe would be complete without mentioning his love of art. He knows an enormous amount about the subject and attends art shows and exhibits all over the world. His personal collection is rich in Dale Chihouly glass and Frank Stella graphics (Figure 3).

Michael Brown was born in Brooklyn, and the family moved to Philadelphia when Mike was eleven. His father, Harvey Brown, was in the wholesale textile business, and his mother, Evelyn Katz Brown, worked at the Smith Kline research laboratories. At age 13 Mike became fascinated with ham radio (and with the construction of radios) and with journalism (Figure 4). At about this time he met Alice Lapin, his first and continuing sweetheart (Figure 4). He won a prize in a high school science competition in Philadelphia, and, influenced by reading Sinclair Lewis' *Arrowsmith*, he wrote on his application to the University of Pennsylvania that he wanted to do medical research. Like Joe, he is a prophet not without honor on his home turf, Cheltenham High School (Figure 4). At Penn, he obtained an undergraduate scholarship, became editor-in-chief of the *Daily Pennsylvanian*, and was elected to Phi Beta Kappa. He then attended the University of Pennsylvania Medical School. Mike was the top student in his medical school class and is shown in Figure 4 making rounds at the University of Pennsylvania Hospital. Jim Wyngarden came to Penn as Chairman of Medicine in Mike's senior year and was an active backer of Mike's application for a residency at the MGH.

As a student Mike spent three summers working at Smith Kline on a project designed to develop agents for the treatment of peptic ulcer. In the course of this work he developed a novel technique for the assessment of gastrointestinal motility (9). His long-term interest in gastroenterology can be traced to this experience. His commitment to science was solidified during a rotation in Albert Winegrad's laboratory, where he studied lipid biosynthesis.

Mike and Joe met on the first day of internship and immediately became friends. At first, most of their conversation had to do with their patients and with medicine. Playing bridge and then duplicate bridge together and studying bidding systems allowed them to develop confidence in each other's judgment.

Figure 4
Mike Brown, a Philadelphia ham radio enthusiast, met his future wife, Alice Lapin, at an early age. He was a hero of Cheltenham High School and is shown making rounds as a student (third from the right) at the University of Pennsylvania, where he was number one in the class of 1966.

Mike also went to the NIH in 1968, where he investigated the use of intestinal biopsies for diagnosis of inborn errors of metabolism and then worked in the Stadtman laboratory, where he discovered that the same enzyme that activates glutamine synthetase can also inactivate the enzyme, depending on whether it is uridinylated (10).

Joe was a good proselytizer for UT Southwestern (of which Mike was previously unaware), and after soul searching (and with some reservations), Mike decided in 1971 to come to Dallas for a fellowship in gastroenterology. He spent most of the first year in clinical duties and learning endoscopy, but he also worked in the laboratory. He initially studied intestinal lymph transport with John Dietschy and then decided to study HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. Mike discovered that the enzyme is

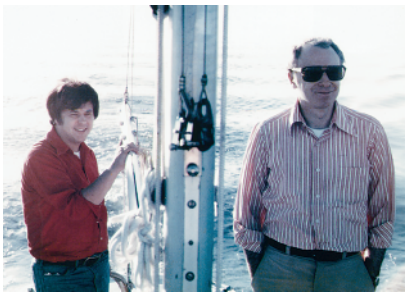

Figure 5
Mike Brown, the sailor at the helm, as his passenger, Joe Goldstein, looks into the future.

Figure 6
Mike Brown, together with his daughters, Sara and Elizabeth, and his wife, Alice Lapin Brown, on the occasion of the graduation of Dr. Elizabeth Brown from the University of Pennsylvania Medical School in 2000.

cold-labile, and he solubilized and partially purified the liver enzyme (11) (at the same time helping run the endoscopy service at Parkland Hospital). By the time Joe Goldstein came back to Dallas in 1972 to set up a medical genetics division, Mike was an important member of the department.

Mike is a fisherman and sailor (Figure 5) and is devoted to his family (Figure 6). He is shown here with Alice and his daughters Elizabeth and Sara on the occasion of the graduation of Dr. Elizabeth Brown from the University of Pennsylvania Medical School.

The collaboration begins

Initially, Mike and Joe had separate laboratories in the department, Mike in the Division of Gastroenterology and Joe in the Division of Medical Genetics. However, their interests overlapped, and they decided to collaborate in studying familial hypercholesterolemia. At NIH they had seen a girl with profound hypercholesterolemia who had had a myocardial infarction at age 6, and they were familiar with evidence suggesting that the severe form of the disease might be due to homozygosity of the mutant gene. At the time almost nothing was known about the pathophysiology of autosomal dominant disorders, and since HMG CoA reductase is the site of cholesterol negative feedback regulation of hepatic cholesterol synthesis, they decided to combine Mike's experience in assaying this key enzyme with Joe's expertise in the culture of skin fibroblasts. They initially demonstrated that HMG CoA reductase activity in control fibroblasts is regulated by lipoproteins in the culture medium (12), and then a telephone call came to Marvin Siperstein (who was in Switzerland) from Thomas Starzl, who was about to operate in Denver on a child with severe hypercholesterolemia (subsequently shown to be due to the receptor-negative form of homozygous familial hypercholesterolemia) (13). The secretary referred the call to Mike, who flew to Denver and returned with a skin biopsy for the growth of fibroblasts, and the rest is history.

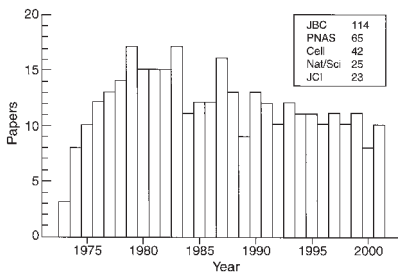

Figure 7
Peer reviewed publications by Mike Brown and Joe Goldstein, 1973–2001.

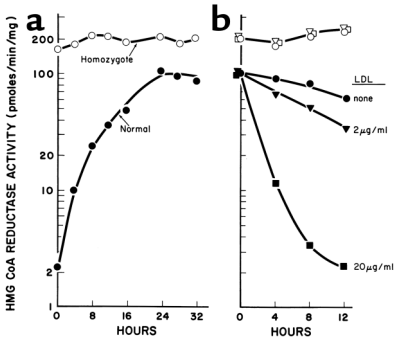

Figure 8
Regulation of HMG CoA reductase activity in fibroblasts from a normal subject (open symbols) and from a FH homozygote (closed symbols). (**a**) Fibroblast monolayers were grown in 10% fetal calf serum, and on day 6 after plating (day 0) the medium was replaced with medium containing 5% human serum from which lipoproteins had been removed. At the times indicated, extracts were prepared, and HMG CoA reductase activity was measured. (**b**) 24 hours after changing to medium containing lipoprotein-deficient serum, human LDL was added to give the indicated cholesterol concentrations, and HMG CoA reductase activity was measured in cell-free extracts at the indicated times (Reprinted from ref. 13).

Paydirt

It is a daunting task to summarize the more than 400 research papers that have come from the Brown and Goldstein laboratory since 1973, a productivity that continues at a remarkably constant level (Figure 7). The critical experiment done in fibroblasts grown from Starzl's patient with homozygous FH is shown in Figure 8 (13). In panel 8a, the activity of HMG CoA reductase, the rate-limiting enzyme in cholesterol synthesis, was measured after incubation of fibroblasts in medium devoid of lipoproteins. No change was seen in the top curve, the patient fibroblasts, which had basal activity some 200% greater than control cells. In contrast, cells from controls, bottom curve, showed brisk increase in HMG CoA activity after incubation in the absence of inhibiting lipoproteins. In Figure 8b is shown the effect of addition of low-density lipoproteins at concentrations of 2 and 20 μg/ml. Normal fibroblasts showed the expected feedback inhibition, while there was no inhibition in the FH fibroblasts.

The findings from the first phase of the studies are summarized in Figure 9 (reviewed in refs. 14 and 15). Low-density lipoprotein (LDL) containing cholesterol ester and protein binds to a cell surface receptor — the LDL receptor — located in a coated pit. This area then pinches off to form a coated vesicle which carries the LDL to the lysosome where it is degraded with the release of amino acids and cholesterol. The released cholesterol serves as a "second messenger" and has at least three effects: decreased HMG CoA reductase activity (the consequence of decreased synthesis and increased degradation of the enzyme), increased esterification of cholesterol due to enhanced activity of acyl CoA: cholesterol acyltransferase (ACAT), and decreased synthesis of the LDL receptor.

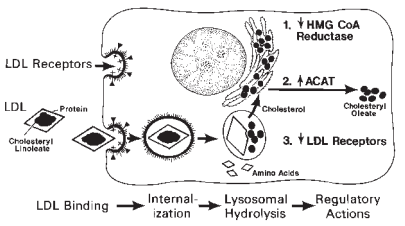

Figure 9
Sequential steps in the LDL receptor pathway of mammalian cells. LDL, low density lipoproteins; HMG CoA reductase, 3-hydroxy-3-methylglutaryl coenzyme A reductase; ACAT, acyl-CoA: cholesterol acyltransferase. (Reprinted from ref. 15.)

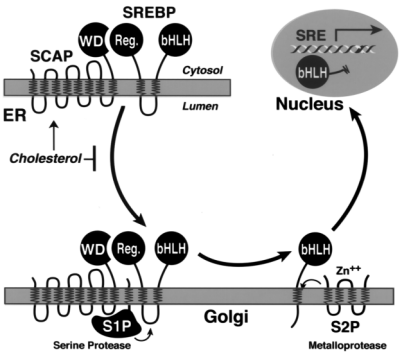

Figure 10
Model for the cholesterol-mediated proteolytic release and processing of sterol regulatory-element binding proteins (SREBPs) from membranes. ER, endoplasmic reticulum; SCAP, SREBP clevage-activating protein contains regulatory (reg) and basic helix-loop-heliz (bHLH) domains; S1P and S2P, site 1 and site 2 proteases (modified from reference 16).

Familial hypercholesterolemia is due to mutations in the gene that encodes the LDL receptor, the heterozygous state being less severe than the homozygous state. The overall mechanism by which LDL cholesterol is internalized and processed was named receptor-mediated endocytosis, a process subsequently shown to be responsible for the internalization of many different molecules from plasma. Discovery of receptor-mediated endocytosis was a monumental accomplishment.

The initial studies had established that cholesterol essentially functions as a "second messenger" in control of cholesterol synthesis. Brown and Goldstein have now worked out the signaling system by which cholesterol transmits its messages, a system termed the sterol regulatory-element binding protein (SREBP) pathway (Figure 10) (reviewed in ref. 16). Critical components of the system include SREBP cleavage-activating protein (SCAP) and Site 1 and Site 2 proteases (S1P and S2P). The start site is the endoplasmic reticulum where SCAP is a sensing element for cholesterol and is bound to the regulatory domain of SREBP. When the cell is replete with cholesterol, the SREBP/SCAP complex remains in the endoplasmic reticulum, and SREBP is not activated by proteolysis. A decrease in the intracellular level of cholesterol is sensed by SCAP, and the SCAP/SREBP complex moves to the Golgi apparatus. There the S1P protease clips the hydrophilic hairpin loop, allowing the basic-helix-loop-helix (bHLH) transcription factor domain to migrate to the S2P, which cleaves it within the transmembrane helix. The bHLH domain then moves into the nucleus, where it binds to the sterol regulatory element and initiates transcription of cholesterol responsive genes that encode the LDL receptor, HMG CoA reductase, and other enzymes of lipid synthesis. As in the case of receptor-mediated endocytosis, the SCAP/SREBP system expanded far beyond cholesterol and is now known to control the regulation of at least 30 genes involved in lipid metabolism.

In 1985 Brown and Goldstein were awarded the Nobel Prize for Medicine or Physiology for their discovery of receptor-mediated endocytosis. They are the eighth and ninth members of the AAP who have won both the Nobel Prize and the Kober Medal (Table 1). In an article in Science describing their Nobel Prize, Arno Motulsky made a prophetic comment: "Considering their past record, the scientific community is eagerly awaiting their future work" (17). Not only has their subsequent work been as exciting as the early studies, but, more importantly, we still eagerly await their future work.

Figure 11
Mike and Joe enjoy their celebrity status, including the opportunity of meeting President Reagan in the White House, Prime Minister Shamir of Israel in his office, and Prime Minister Margaret Thatcher of the United Kingdom in their office.

The academic citizens

Mike and Joe are exemplary academic citizens. Their record of mentorship includes the training of 10 Ph.D. and 11 M.D./Ph.D. students and 87 postdoctoral fellows. Nineteen of their trainees are full professors: 3 in departments of medicine; 16 in basic science departments or research institutes. Two, Helen Hobbs and Sandra Hofmann, are members of AAP. Three are Howard Hughes Medical Institute investigators. Four are scientific directors at biotechnology companies. Two, Thomas Sudhoff and Xiaodong Wang, have received major awards for their work in the fields of neuroscience and programmed cell death, respectively. At the same time, Brown and Goldstein are dedicated members of the faculty — helping to recruit to many departments, raising funds for the school, serving on committees for the benefit of the institution, and directing the medical scientist–training program. Their loyalty to Southwestern never wavers, and everyone who knows them profits from their wise counsel. At the national level their impact is similarly important — including service on boards of regents, prize committees, and granting agencies.

Figure 12
Joe and Mike "hamming it up" at a laboratory party.

It is also appropriate to commend some of the non-academic sides of Brown and Goldstein. They have an enormous zest for life. They enjoy their status as celebrities and the rewards that go with such status

Table 1
Winners of both the Nobel Prize and the George M. Kober Medal

Winner	Nobel prize	Kober medal
George M. Minot	1934	1929
George H. Whipple	1934	1939
Edward C. Kendall	1950	1952
Peyton Rous	1966	1953
Herbert S. Gasser	1944	1954
Dickinson W. Richards	1956	1970
E. Donnall Thomas	1990	1992
Michael S. Brown	1985	2002
Joseph L. Goldstein	1985	2002

Figure 13
Le Chateau des Pyrenees (The Castle in the Pyrenees) by Rene Magritte. 1959. Reprinted with the permission of the Artists Rights Society.

(Figure 11). They are both dedicated party animals and party givers, as indicated by the elaborate skits they perform (Figure 12). They approach every endeavor with the same enthusiasm they apply to science, they enjoy themselves, and they are the best of company.

Conclusion

Mike Brown and Joe Goldstein have won many prizes, honorary degrees, recognitions, and fame, but their receipt of the Kober Medal is uniquely appropriate because of the impact that they have had on the Association and on the American Society for Clinical Investigation. Beginning in 1974, when they presented to the plenary sessions of both organizations, Mike and Joe (and their trainees) have made 14 plenary session and state-of-the-art lectures at these meetings (not counting presidential and after-dinner addresses). This record is unequalled in modern times.

Joe Goldstein's favorite painter is the Belgian surrealist René Magritte, and the 1959 Magritte painting entitled "*The Castle in the Pyrenees*" is appropriate to commemorate this occasion (Figure 13). The title is a word play on the French version of "*Castles in the Sky*," and the painting is believed to derive from a story by Edgar Allen Poe in which a semi-Gothic structure appeared to be suspended in mid air (18). Mike and Joe built a phenomenal castle in the sky, and they built it on the solid foundation of a remarkable collaboration. In so doing, they revolutionized biomedical science and developed a new paradigm for the conduct of research. It is a pleasure and an honor to present, on behalf of the Council of the AAP, the 2002 Kober medals to Michael S. Brown and Joseph L. Goldstein (Figure 14).

Figure 14
Joseph L. Goldstein and Michael S. Brown in Stockholm at the time of their receiving the 1985 Nobel Prize for Medicine or Physiology.

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