The 1982 John Scott Award Goes to
Jack Fishman and Harold Blumberg for
Synthesis and Investigation of Naloxone

On April 11, 1983, the Philadelphia Board of Directors of City Trusts awarded the 1982 John Scott Award jointly to Jack Fishman, Rockefeller University, and Harold Blumberg, New York Medical College, Valhalla, for research on naloxone (N-allyl-14-hydroxydihydro-nor-morphinone), a narcotic antagonist. The award was presented at a session of the American Society for Pharmacology and Experimental Therapeutics held during the annual Federation of American Societies for Experimental Biology (FASEB) meeting in Chicago.

As a member of the John Scott Award Advisory Committee, I had the pleasure of preparing and reading the citation.[1] In the citation, I pointed out Fishman and Blumberg's contributions—Fishman synthesized naloxone and Blumberg determined that naloxone was a "potent, rapid-acting, and relatively pure narcotic antagonist." The citation went on to note that naloxone is "now the treatment of choice in reversing narcotic effects, and has also become an essential tool in the discovery and investigation of endogenous opioids." In addition, the citation summarized the outstanding careers of these two scientists. Randall M. Whaley, president, University City Science Center, Philadelphia, and secretary of the Advisory Committee, then presented the award. The John Scott Award includes a medal (see Figure 1) and a certificate, as well as an honorarium of about $3,000 for each corecipient.

This annual award, established in 1816 by John Scott, an Edinburgh chemist, is intended for "ingenious men and women who make *useful* inventions."[2] Previous recipients include Marie Curie, Orville Wright, Thomas Edison, Alexander Fleming, Jonas Salk, R. Buckminster Fuller, and Sir James Whyte Black.

The discovery of naloxone amply fulfills the usefulness criterion of the John Scott Award. It was not the first narcotic antagonist to be synthesized, nor is it the most potent. But naloxone's special biological properties have dictated significant clinical and research roles for it, far beyond those envisioned by its early developers.

Naloxone's primary clinical application is in reversing the reduced respiration caused by natural and synthetic opiate-like substances.[3] This means naloxone can counteract a heroin overdose, as well as reverse the effects of narcotics used in surgical anesthesia. Naloxone can also reverse the effects on a newborn child of narcotics originally given to the mother during labor. Furthermore, naloxone is used in diagnosing comas of unknown origin to determine if narcotic overdose is involved.

Although naloxone is used almost routinely wherever narcotic research is performed, the drug's primary research application is in the study of endogenous opioids—naturally occurring, morphine-like substances. Naloxone has played an essential role in the exploration of this recently discovered physiological system.

Understanding naloxone's significance requires some knowledge of narcotic antagonist and agonist action. To review briefly, a narcotic antagonist
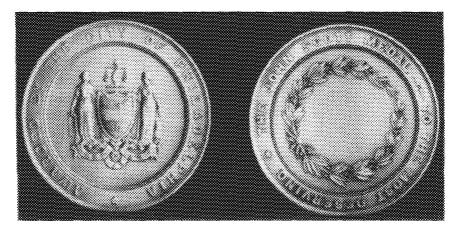
Figure 1: The John Scott Medal awarded to Fishman and Blumberg by the Philadelphia Board of Directors of City Trusts.

counteracts the effects of narcotic agonists such as morphine, heroin, and meperidine.[4] These agonists interact with receptor sites in the brain to cause such physiological responses as analgesia (pain reduction), reduced respiration, drowsiness, constricted pupils, euphoria, sedation, and nausea. Antagonists usually function by competing with the agonist for receptor sites, thus minimizing or eliminating agonist effects. Although they counteract agonists, they may themselves produce some agonistic effects, including analgesia. But in general, they do not cause a narcotic type of physical dependence, although in some cases they may produce a milder type of dependence.

The first clinically useful antagonist was nalorphine (*N*-allylnormorphine), a derivative of morphine.[5] In morphine-related compounds, antagonist activity appears to be a function of the alkyl group attached to the nitrogen atom. In nalorphine, the substituent methyl group in morphine is replaced with an allyl group, which confers antagonist properties (see Figure 2). As an antagonist, nalorphine was found to be effective in counteracting narcotic overdose. At higher doses it caused analgesia as well. Unfortunately, along with its analgesic properties, nalorphine was shown to cause hallucinations and reduced res-

piration, among other negative agonist effects. Although these negative effects detracted from nalorphine's usefulness as an analgesic, the drug did inspire research on a wide range of related compounds.[4-6] The goal of this research was twofold: finding a nonaddicting analgesic with the perfect balance of agonist and antagonist effects, and finding a potent narcotic antagonist without adverse side effects. Naloxone, one result of this search, proved to be the desired narcotic antagonist.

The John Scott Award recognizes two key but previously unacknowledged events in naloxone's development: its original synthesis by Fishman and its significant biological investigation by Blumberg. Research on naloxone has proliferated over the past two decades, and many scientists have helped elucidate its properties. But these initial steps laid the foundation for all further progress. Ironically, the two men responsible were unknown to each other when naloxone was first synthesized in 1960, although both were in close communication with a third person, Mozes J. Lewenstein. Lewenstein was the head of the Endo Laboratories narcotics division and also had a small private laboratory of his own. Endo, then located in Richmond Hill, New York, is now a division of the biochemicals department of E.I.
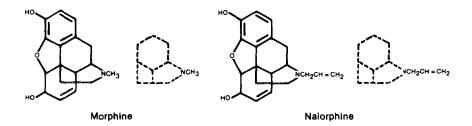
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Morphine   Nalorphine

Figure 2: Structural relationship of morphine to nalorphine.

du Pont de Nemours & Company, Inc., and is located in Wilmington, Delaware. Endo has been renamed Du Pont Pharmaceuticals.

At the time of naloxone's synthesis, Fishman was an assistant (later an associate) in steroid chemistry and biochemistry at the Sloan Kettering Institute for Cancer Research, New York. He was also employed in Lewenstein's private laboratory, which was licensed for narcotics research. To avoid conflict between his two jobs, Fishman confined his work for Lewenstein to narcotic alkaloid chemistry. He had had some experience in this field, as his PhD thesis involved both steroid and alkaloid research.

In 1960, Blumberg was director of biological laboratories at Endo, and was soon to become associate director of research. As early as 1956, he had been urging Endo researchers, including Lewenstein, to synthesize an antagonist analogous to nalorphine using oxymorphon⁄, a synthetic morphine analogue ten times as potent as morphine.[7] Since nalorphine was derived from morphine, Blumberg speculated that an antagonist could be derived from oxymorphone. However, this new drug could conceivably have ten times the narcotic antagonist or analgesic property of nalorphine, while retaining the essentially nonaddictive character of an antagonist. Its high potency might permit lower dosages, reducing unwanted side effects.

Although this idea was not pursued at Endo, Fishman later synthesized the compound at Lewenstein's private laboratory. Using reasoning similar to Blumberg's, Fishman tried to combine the 14-hydroxy (potent analgesic) function of oxymorphone (14-hydroxydihydromorphinone) with the N-allyl (antagonist) function of nalorphine (see Figure 3).[8] Uncertain about the new compound's usefulness, Lewenstein licensed the drug to Endo for evaluation. Blumberg, recognizing the drug that had interested him earlier, promptly began testing its biological properties in animals. But the results disappointed those hoping for the ultimate analgesic.

In the first published work on naloxone, a 1961 abstract in *Federation Proceedings*,[9] Blumberg and his colleagues reported that naloxone was a potent narcotic antagonist. It counteracted the effects of morphine, dihydromorphinone, meperidine, methadone, and phenazocine. However, it showed no analgesic activity of its own. Nevertheless, its efficacy as an antagonist warranted a patent. Lewenstein and Fishman applied for a patent in March 1961,[10] stating that naloxone and its salts are "more potent antagonists to the respiratory depressive effects of potent analgesics than the antagonists hitherto known." At the time, however, a potent antagonist appeared to have more academic than commercial value.

In 1965, further tests of naloxone's antagonistic activity in rats indicated that it was at least 15 times as potent as nalorphine against morphine, meperidine, and oxymorphone.[11] A major breakthrough came in 1966,[12] in tests of nalox-
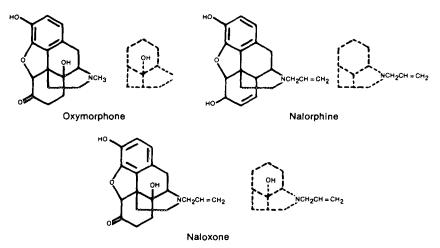
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Figure 3: Structural relationship of oxymorphone and nalorphine to naloxone.

one's action against the *analgesic* activity of other narcotic antagonists, including nalorphine, pentazocine, and cyclazocine. Naloxone counteracted the analgesic activity of all these drugs while showing no analgesic activity of its own. For practical purposes, it was a "pure" narcotic antagonist at therapeutic doses. This study established that not only was naloxone quantitatively more potent than all previously known narcotic antagonists, it was qualitatively different as well. Studies carried out that same year[13] showed that, although naloxone was about 15 to 30 times as active as nalorphine, it had comparatively low toxicity. It showed toxic effects only at doses far higher than the normal therapeutic dose. This first chapter in naloxone research clearly established the biological properties determining the drug's use.

What I find especially interesting about the history of naloxone is that the original synthesis of this important compound was first disclosed in a patent[10] rather than in a journal article. The first full-length journal article mentioning research on naloxone was published by a group working for Sankyo Company in Japan, in 1962,[14] a year after Blumberg published his abstract[9] and Lewenstein

and Fishman applied for their patent for naloxone.[10] Sankyo holds a British patent for naloxone, which was applied for in March 1962 and issued in October 1963.[15]

In cases like these, absolute priority is difficult to determine. But it seems clear that Lewenstein (listed as senior author on the patent, but now deceased), Fishman, and Blumberg are now acknowledged as the early developers of naloxone. The consensus for this view is supported by a search of the patent and journal literature. Whereas almost 100 patents and articles refer to the US patent and Blumberg's 1961 abstract, there is but one reference to the 1962 paper from Sankyo in the *Science Citation Index*® (*SCI*®).

The initial scarcity of journal articles on a compound of naloxone's significance may be explained by a number of factors. For one thing, Fishman didn't want to jeopardize Lewenstein's efforts to obtain a patent by publishing. In addition, commercial considerations frequently constrain detailed publication. But the underestimation of naloxone's importance may have also played a role. Naloxone was easy to overlook, because researchers were intent on developing analgesics. The unique effectiveness and

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safety of naloxone as a narcotic antagonist were not really appreciated until publication of Blumberg's 1966 paper,[12] which has since been cited in at least 66 publications. Furthermore, the whole field of endogenous opioids, which later relied heavily on the use of naloxone, was not yet conceived. Finally, Fishman's primary concern was steroid rather than alkaloid chemistry, so he did not feel compelled to publish on naloxone.

Fishman, who was born in Poland in 1930, began his career in organic chemistry with a BA degree from Yeshiva University, New York, in 1950. He received an MA from Columbia University in 1952 and a PhD from Wayne State University, Detroit, in 1955. In addition to working at the Sloan Kettering Institute, he has worked at Albert Einstein Medical College and served as director of the Institute for Steroid Research, Montefiore Hospital, Bronx, New York. In 1977, he became an adjunct professor at Rockefeller University, while retaining his appointment at Albert Einstein. He joined Rockefeller University full-time in 1980 as professor and head of the laboratory of biochemistry and endocrinology.

Fishman is active in several professional societies and serves on the editorial boards of a number of journals. His memberships include Sigma Xi, the American Chemical Society, the American Society of Biological Chemists, and the Endocrine Society, where he has chaired the Scientific Affairs Committee. Fishman has been a member of the editorial board of the *Journal of Clinical Endocrinology and Metabolism*, and is currently on the boards of the *Journal of Steroid Biochemistry* and *Pharmacology*.

He has also served on special boards and commissions such as the Scientific Advisory Board of the National Center for Toxicological Research, from 1976 to 1978; the National Institutes of Health (NIH) Task Force on Cancer, from 1978 to the present; and the Endocrinology Study Section of NIH, of which he is now the chairman. In 1976 he went to the People's Republic of China with the US Steroid Chemistry and Biochemistry Delegation. In 1980, he held a visiting professorship in Japan, sponsored by the Japan Society for the Promotion of Science.

In the course of his career, he has served as a consultant to the National Institute on Aging, the Food and Drug Administration (FDA), the Contraceptive Development Branch of NIH, the World Health Organization, the National Research Council of Canada, and the National Science Foundation.

Fishman's major scientific contributions have been in the chemistry, biochemistry, and biology of estrogens. He has identified the mechanism of estrogen biosynthesis from androgens and elucidated the pathways of estrogen metabolism in the human. In the course of the latter work, he discovered one category of metabolites known as the catechol estrogens, which appear to have important functions in mammalian physiology. Fishman is particularly concerned with the role of estrogens in disease states, including breast and endometrial cancer. A recent paper focuses on the action of 16α-hydroxyestrone in lupus erythematosus.[16] Estrogens are implicated in this disease because it tends to occur nine times more often in females than in males.

Of course, alkaloid chemistry has been of much more than incidental interest to Fishman. In addition to naloxone, he synthesized approximately 15 related agonists and antagonists while working for Lewenstein. Subsequently, he explored ways to prolong naloxone's action[17-19] and also traced its disposition in humans.[20,21] An area of particular concern in Fishman's alkaloid research is the chemical characteristics that distinguish antagonists and agonists.[22-25] Fishman theorizes that removal of the alkyl substituent on nitrogen by enzymes in the brain is responsible for agonist activity. Fishman's most recent work in alkaloid chemistry is on the clinical application of naloxone in treating gastrointestinal disorders.[26]

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Fishman's two specialty areas have converged over the years, as evidence has mounted for a role for endogenous opioids in endocrine function. In the past decade, he has published several papers on the relationship of opiates to the endocrine system.[27-30]

A recent check of *SCI* demonstrated the impact of Fishman's publications on a variety of subjects. Fishman now holds one of the top 2,000 rankings for primary authors. In fact, in 1980 and 1981, one of Fishman's papers[31] appeared as a core paper in two *ISI/BIOMED®* research fronts—"Binding response of catechol-estrogens to hormone secretion" and "Regulatory components of adenylate-cyclase and cholera toxin-dependent ADP-ribosylation."

In contrast to Fishman, whose primary field is steroid chemistry, Blumberg has specialized in narcotic pharmacology since the invention of naloxone. During this time, however, he was also a codiscoverer of the antipsychotic drug molindone. Blumberg was born in 1909 in West Virginia, and did his undergraduate work in chemistry and biology at West Virginia University, Morgantown, and at Johns Hopkins University, Baltimore. In 1933, he received his ScD in biochemistry and toxicology from Johns Hopkins University School of Hygiene and Public Health. His early academic career included faculty positions at Johns Hopkins in the department of pediatrics of the School of Medicine, where he published a series of papers on lead poisoning, and in the department of biochemistry of the School of Public Health, where he did research on the value of choline in treating fatty cirrhosis of the liver. In 1934-1935, while at Johns Hopkins, he was awarded a National Research Council Fellowship in Medical Sciences. He has also held positions as a biochemist with the US Public Health Service, Washington, DC, and as a toxicologist with the US Army Industrial Hygiene Laboratory, Baltimore. Blumberg began working in private industry in 1944, as senior biologist for the Sterling-Winthrop Research Institute, Rensselaer, New York. He became director of biological laboratories at Endo in 1947 and in 1960 was made associate director of research. Blumberg returned to the academic world in 1974 as research professor of pharmacology at New York Medical College. In 1981, he became research professor emeritus. Since 1974, he has served as a consultant to the National Institute on Drug Abuse of the US Public Health Service.

Blumberg is a member of the American Society for Pharmacology and Experimental Therapeutics, the Society of Toxicology, the Society for Experimental Biology and Medicine, and the American Institute of Nutrition. He is an honorary member and a past president of the Parenteral Drug Association.

In addition to Blumberg's research on lead poisoning, choline, and antipsychotic drugs, his numerous publications include work on antispasmodics and anticoagulants. Since 1960, he has published primarily on narcotic analgesics, antagonists, and antagonist analgesics. In addition to naloxone, these studies focus on two closely related compounds, nalbuphine and naltrexone. Nalbuphine is an antagonist analgesic that is practically as potent as morphine when injected.[32,33] But because of its antagonist properties, it carries little or no addiction liability. It does cause slight side effects, including reduced respiration, but these appear to reach a plateau rather than increase with increasing dosage. Naltrexone is an even more potent antagonist than naloxone, although it may have some clinically insignificant agonist properties.[34,35] Naltrexone compensates for some of naloxone's shortcomings by being longer-acting, as well as more effective when administered orally. Naltrexone is currently under investigation for use in the rehabilitation of narcotics addicts.[36] Blumberg has informed me that a license for this use has been applied for with the FDA.[37]

Through the early-1970s, Fishman and Blumberg's work on naloxone, as well as that of most other researchers, was directed toward clinical applications. I've

already mentioned naloxone's effectiveness in reversing narcotic overdose. In a related use, naloxone is often given to treat comas of unknown origin. In these cases, naloxone is both a therapeutic and a diagnostic tool. If a coma is caused by narcotics, naloxone will reverse it within a few minutes, revealing the coma's cause. If narcotics aren't involved, naloxone will have no effect. It won't help patients but it won't harm them either, because of its low toxicity and lack of respiration-reducing action. But though naloxone is used routinely in a number of hospitals to treat comas of unknown origin, some researchers do urge caution.[38]

Naloxone is also commonly used after surgery to hasten a patient's arousal from anesthesia. Often, narcotics are given in conjunction with general anesthesia to reduce the dose of anesthetic required. After surgery, injection of naloxone immediately reverses narcotic effects. In addition, naloxone can be given to reverse narcotic analgesia administered for uncomfortable diagnostic procedures such as endoscopy. In newborns, naloxone reverses reduced respiration caused by narcotics given to the mother for anesthesia during labor.[39] However, naloxone is not a substitute for customary resuscitation efforts, and must be used cautiously in narcotic-dependent individuals.

When naloxone's potent antagonism was identified in animal[9,11-13] and human studies,[40,41] researchers envisioned a role for it in curing narcotic addiction. Injection with naloxone counteracts the euphoric agonist effects of narcotics and induces withdrawal in an addicted person. But this application has proved impractical because of the short duration of naloxone's action (a few hours) and its poor effectiveness when administered orally. Naloxone appears to enter the brain readily. It is then rapidly excreted.[20] When administered orally, most of it is converted to an inactive form. An addicted person using naloxone would probably require constant supervision. A number of attempts have been made, including those by Blumberg[42] and Fishman,[17-19] to prolong naloxone's action by developing a slow-release form. But none has proved practical. Again, naltrexone has replaced naloxone as the antagonist used in addiction therapy studies.[36] However, small repeated injections of naloxone have been used for rapid detoxification of narcotics addicts in 24 to 48 hours, instead of the usual ten to 14 days.[43]

Naloxone may have an ingenious application in preventing the diversion of legal drugs to street use. On the street, injection is the preferred way to take narcotics. A patent was issued in 1973 for an analgesic combination composed of an orally inactive dose of naloxone and an orally active strong analgesic.[44] The proportions are carefully balanced so that, if injected, the antagonist will be activated and negate the effects of the agonist. A person injecting this combination will not experience a "high." But when legitimate users take the combination orally, as intended, they'll experience analgesia. One of the inventors on this patent is my old friend Maxwell Gordon, one of the earliest supporters of *Index Chemicus*® and now senior vice president of science and technology at Bristol-Myers Company. In a similar application of an analgesic-antagonist combination, Sterling Drug Inc. was recently reported to be reformulating its pentazocine (Talwin) prescription oral pain reliever to incorporate naloxone.[45] In this way, the company hopes to combat the popular street practice of injecting a combination of Talwin and tripelennamine, an antihistamine.

In addition to these clinical applications, naloxone's relative purity as a narcotic antagonist has conferred on it a unique role in endogenous opioid research. Several researchers have testified to naloxone's significance in this field. According to Lars Terenius, Uppsala University, naloxone has been "the most useful single tool for the study of endogenous opioids."[46] John Hughes, Imperial College of Science and Technology, London, states that the theories

he and Hans Kosterlitz, University of Aberdeen, formulated "were considerably influenced by the properties of naloxone."[47]

Although the major effects of narcotic opiates such as morphine have long been known, until recently little was understood about their mode of action. But in the early-1970s, researchers proved the existence of "opiate receptors" for these drugs in animal nervous tissue.[48-52] This was followed in 1975 by the discovery of *endogenous* opioid substances which bind to these receptors, opiate peptides known as enkephalins.[53] Naloxone was employed in all these studies to detect opiate activity because it was the purest narcotic antagonist available, having almost no other activity at low doses. Therefore, it was reasoned, any activity or effect it counteracted must be opiate-related.

Research on opiate peptides continues to employ naloxone as the indicator of opiate activity. But limitations on this use have become apparent.[54] At high doses, naloxone has some agonist activity *in vivo* and *in vitro*. Naloxone also appears to respond to some non-opiate drugs. J. Sawynok, University of Manitoba, suggests that naloxone be considered a necessary but not sufficient condition for indicating endogenous opiate activity.[54] Other corroborating evidence must be supplied as well.

Generally speaking, however, opiate peptides and naloxone are two sides of the same coin. What one stimulates, the other tends to inhibit. Insight into the broader physiological function of opiate peptides has provoked new ideas for clinical uses of naloxone. In some situations, excess production of opiate peptides might be considered a disease state, for which naloxone is the cure.

For example, a patent has recently been issued for the use of narcotic antagonists, including naloxone, in reversing many types of shock.[55] The primary characteristic of shock is hypotension (low blood pressure). Naloxone rapidly reverses opiate peptide release, which the authors suspect is hypotension's underlying cause. Naloxone may also play a role in stroke treatment. Naloxone has completely reversed neurological symptoms in two stroke patients for a short period of time,[56] as well as in animals.[57] Research on naloxone and opiate peptides in obesity may also lead to a new application for naltrexone. Naloxone has inhibited weight gain in genetically obese rats[58] and decreased food intake in obese humans.[59] As a result, naltrexone, being a longer-acting and orally more effective antagonist than naloxone, is under study for weight control in humans.[36]

As I mentioned earlier, Fishman has been working on gastrointestinal applications of naloxone. A recent paper he published with Mary-Jeanne Kreek, Rockefeller University, reported successful treatment with naloxone of two patients with chronic constipation.[26] The authors hypothesized that excess opiate peptides or altered opiate receptor function contribute to constipation. Another recent report indicates that naloxone may have at least temporary positive effects on the mental processes of patients with Alzheimer's disease,[60] a condition in which opiate peptides may play a role.

Obviously, these uses represent the first entries in what could become a catalog of opiate peptide reversing applications. If so, much will be owed to Fishman and Blumberg, and others who have done so much basic research. While no one at the time could have recognized how important naloxone would become, the story reveals once again the way in which basic research works to the advantage of mankind. Fishman and Blumberg have had distinguished careers apart from their work with naloxone. But naloxone was an important point of departure for both of them and the John Scott Award Advisory Committee felt that their work ought to be formally recognized.

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