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Current Comments

Controversies Over Opiate Receptor Research Typify Problems Facing Awards Committees

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The announcement of the 1978 Lasker Award for Basic Medical Research has created two controversies. No one argues with the choice of the three winners—Solomon H. Snyder (Johns Hopkins University), John Hughes (Imperial College of Science and Technology, London), and Hans Kosterlitz (University of Aberdeen) —who were honored for the discovery of opiate receptors and enkephalins, opiate-like substances produced by the body. The controversies surround several other researchers who might have appropriately shared the award with the three. The first dispute centers around the exclusion of a junior investigator from the award. The second arises from the exclusion of several independent investigators who had done similar or other essential research in the field.

These disputes are worth discussing because they point up issues which are likely to become all too familiar to scientific awards committees in the future. The 1978 Lasker is merely a case in point. The Lasker's honorarium ($15,000) and its prestige (28 winners have gone on to receive the Nobel) give the award great visibility within the biomedical community. Hence, disputes surrounding it get publicity.

The first controversy over the Lasker was set off by Candace Pert, National Institute of Mental Health (NIMH), when she claimed she had been unfairly omitted from the award-winning group. As a graduate student and a National Institutes of Health (NIH) postdoctoral fellow, she had worked with Snyder on much of the research for which he was honored. In a letter (quoted in *Science*[1]) to Mary Lasker, president of the Lasker Foundation, Pert claimed that she had "played a key role in initiating this research and following it up...." Snyder has supported Pert's claims. He called members of the awards committee and asked them to consider including Pert among the recipients. He also stated publicly that "it would have been appropriate if Pert had shared the award with him."[1]

The dispute arouses suspicions of sex discrimination.[1,2] But if, for the moment, we absolve the committee of prejudice, we can discern another characteristic which is a likely source of the conflict: Pert was a junior member of a research team.

Collaborative research is not new to science, but its increase since the 1950s has been phenomenal. In 1963, Derek de Solla Price was already noting that the number of papers with three authors was increasing faster than those with two. And the number of four-author papers was increasing more rapidly than the number of those with three.[3] (p. 88)

This growth is also reflected in the number of prize winners who are honored for collaborative research. Harriet Zuckerman, in her study of Nobel laureates, notes: "During the first 25 years of the awards...just 41% of the laureates were honored for collaborative work... During the second quarter century the proportion jumped to 65%, and it now stands at 79% of all prizewinners."[4] (p. 176)

Zuckerman also indicates that only about one-third of the laureates overall shared their prizes with co-workers—although almost two-thirds of them won for collaborative research. She states that "a sizable number of contributors to prize-winning research do not win...."[4] (p. 178)

Many contributors are passed over for prizes because of their junior status. Although members of some collaborative teams are recognized throughout the scientific community as equals in rank, prestige, and experience, usually one or two scientists on a team are considered "senior," the others junior.

There is no clearcut definition by which a scientist may fall into the junior category. For example, John Hughes, who collaborated as an independent investigator with Hans Kosterlitz, ran his own laboratory. Yet he could easily be seen as junior to Kosterlitz, who is one of the renowned pioneers in opiate research. In fact, Kosterlitz was aware that he might overshadow Hughes. Thus he chose not to appear as an author on the very first paper announcing the discovery of enkephalin, which appeared in *Brain Research*.[5] Hughes, who appeared as the sole author, acknowledged Kosterlitz at the end of the paper. While I can understand Kosterlitz's desire to help a colleague, I think this is a practice which should be avoided.[6]

With only limited information on junior collaborators, awards committees will most likely have to take a conservative stance. They will give the awards to senior investigators, scientists whose previous work and status makes them "known quantities." Committees will ignore junior and relatively unknown collaborators on the principle that it is better to overlook a worthy contributor than to give a prize to someone who does not deserve it. Undoubtedly, this attitude will engender more controversies over the contributions of junior associates.

Pert could protest her exclusion since Snyder, the senior investigator on her team, won the award. Other junior investigators involved in opiate receptor research could not, as their senior investigators were overlooked entirely by the committee. The fact that several people who did important work in the field were bypassed became the source of the second controversy surrounding the 1978 Lasker. Thomas Maren (University of Florida, Gainesville) gave expression to this dispute in a letter to *Science*. He stated that he "(and many others)...are keenly aware of the remarkable progress [in opiate research] made by *five* groups (not two).... Why then was [Goldstein] excluded, as were Terenius of Uppsala and Simon of New York University? All of this work is inextricably linked, as the writings of these men and women have shown continually."[7]

Certainly the omission of these investigators appears arbitrary since they did work vital to the field or made discoveries simultaneously with the Lasker winners. The secrecy of awards committees' deliberations has many advantages. However, this secrecy may also result in the dissatisfaction expressed by Maren over the exclusion of some worthy researchers.

Simultaneous discovery is not unusual in science. Robert Merton, who has written extensively on the phenomenon, has noted that "the pattern of independent multiple discoveries in science is in principle the dominant pattern rather than a subsidiary one."[8] (p. 356) Like collaborative research, simultaneous discovery is a reality which awards committees must confront. If they do not, simultaneous discoveries will be a source of controversy in the years ahead.

We may someday reach a point when award decisions are subjected to confirmation by a world science court. Award committees may have to defend their selections—or rejections. Certainly, the members should prepare, at least, for strong criticism.

As a member of several awards committees myself, I am not pleased by this prospect. In many cases controversy will be unavoidable. However, if committees use all the relevant information available to them, many disputes can be eliminated. Certainly, if greater accountability to the public is required, members of awards committees, like members of corporate boards of directors, will not be cavalier about their responsibilities.

One source of pertinent information available to awards juries is citation data. These data, of course, cannot be used as the sole criterion for making selections. In fact, the Lasker controversies provide a good example of their limitations: Hughes' breakthrough paper, announcing the isolation of enkephalin, was written, as we have seen, without Kosterlitz as a co-author. An awards committee, relying on citation data alone, might have thus overlooked Kosterlitz instead of Pert. However, used properly in conjunction with other information and the original articles, these data can be of invaluable help.

Since the Lasker committee's deliberations are confidential, we do not know if the members used citation data. I doubt that they did. It is interesting to speculate that if they had studied these data, the results might have been different.

For example, the awards committee could have used several of our annual "cluster maps" of active scientific specialties to get an overview of the development of the research.[9] These maps identify highly cited papers from the earlier literature which were frequently cited together ("co-cited") in the more recent literature. The cluster maps are created by using the technique of multidimensional scaling. (See the note at the end of this essay for more details on how cluster maps are generated.)

The first time an "opiate receptor" cluster was identified was in our 1974 data. The map is shown in Figure 1.[10] The papers which comprise the cluster are identified by the first authors' names. A bibliography, giving complete information about the papers in the clusters, begins on the page following the maps.

The 1974 cluster map reveals several important factors which should interest any group wanting to honor the researchers involved in opiate research.

Only one paper (Goldstein 71) was published before 1973. Researchers for at least the past two decades had inferred the existence of opiate receptors from pharmacologic evidence.[11] In fact, earlier papers on the possible existence of the receptors are too numerous to cite. Yet the 1971 paper by Avram Goldstein, Louise Lowney, and B. K. Pal (Stanford University School of Medicine) is in some ways the "parent" of the research which followed. It provided the conceptual framework for physically demonstrating the existence of opiate receptors by distinguishing between nonspecifically and stereospecifically bound radioactive opiates in brain homogenates. This method was refined by later researchers with more success because they used higher affinity opiate ligands of higher radioactivity.

This contribution is of prime importance to research on opiate receptors. And unlike much of the significant later work it is unique: no other scientist or team published a similar paper simultaneously.

Papers announcing the discovery of opiate receptors were published in 1973 by three groups of researchers: Pert and Snyder (Johns Hopkins) in the paper labeled Pert 73(2); Eric Simon, J. M. Hiller, and I. Edelman (New York University); and Lars Terenius (Uppsala Univ.). Simon's and Snyder's labs reportedly made their discovery "almost

Figure 1. 1974 Cluster Map: Opiate Receptors

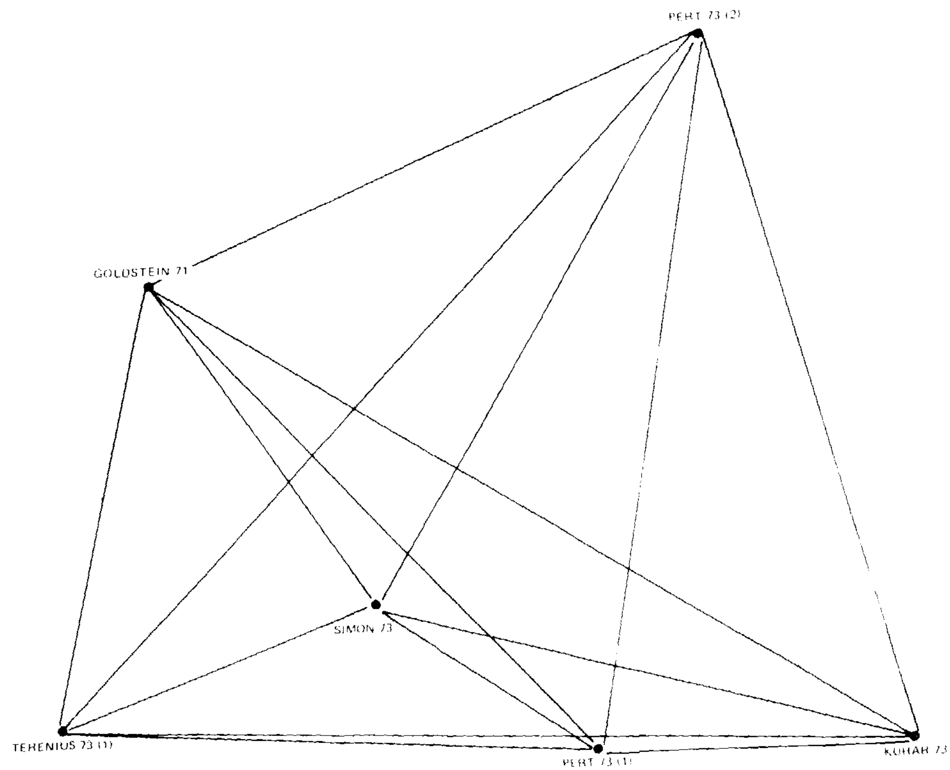


Figure 2. 1975 Cluster Map: Opiate Receptors

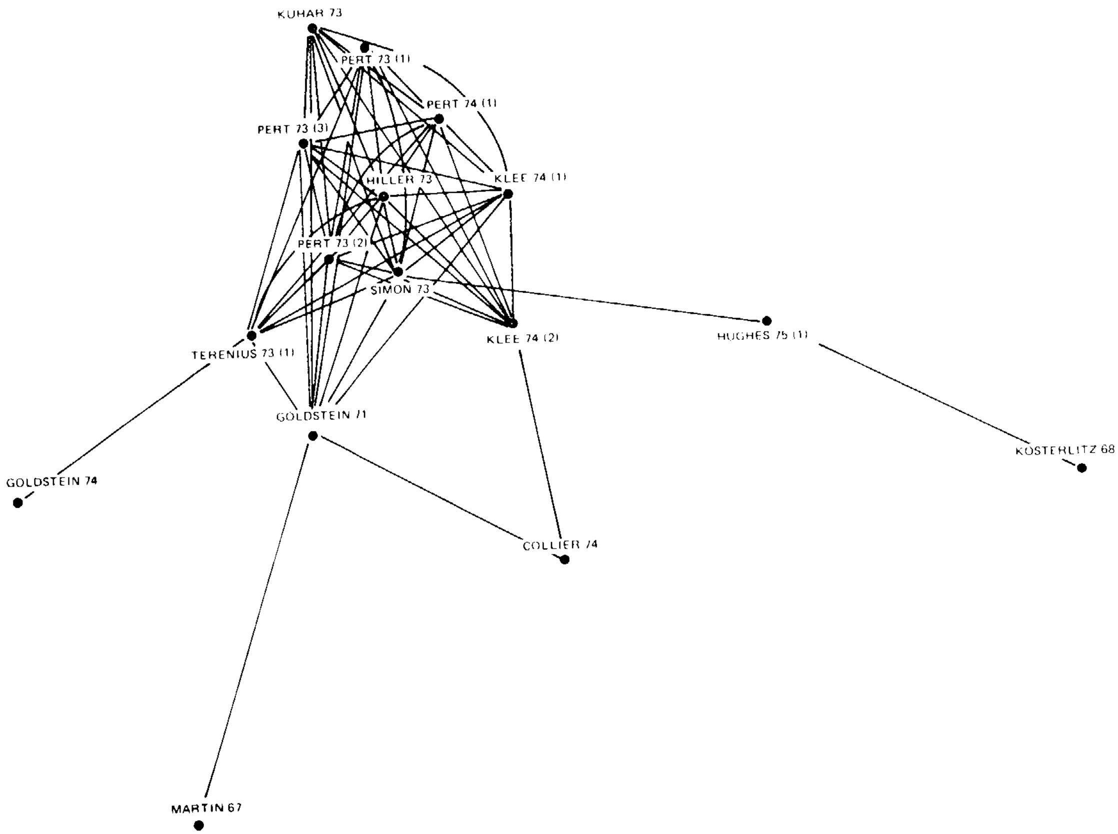


Figure 3. 1976 Cluster Map: Opiate Receptors and Endogenous Opiates

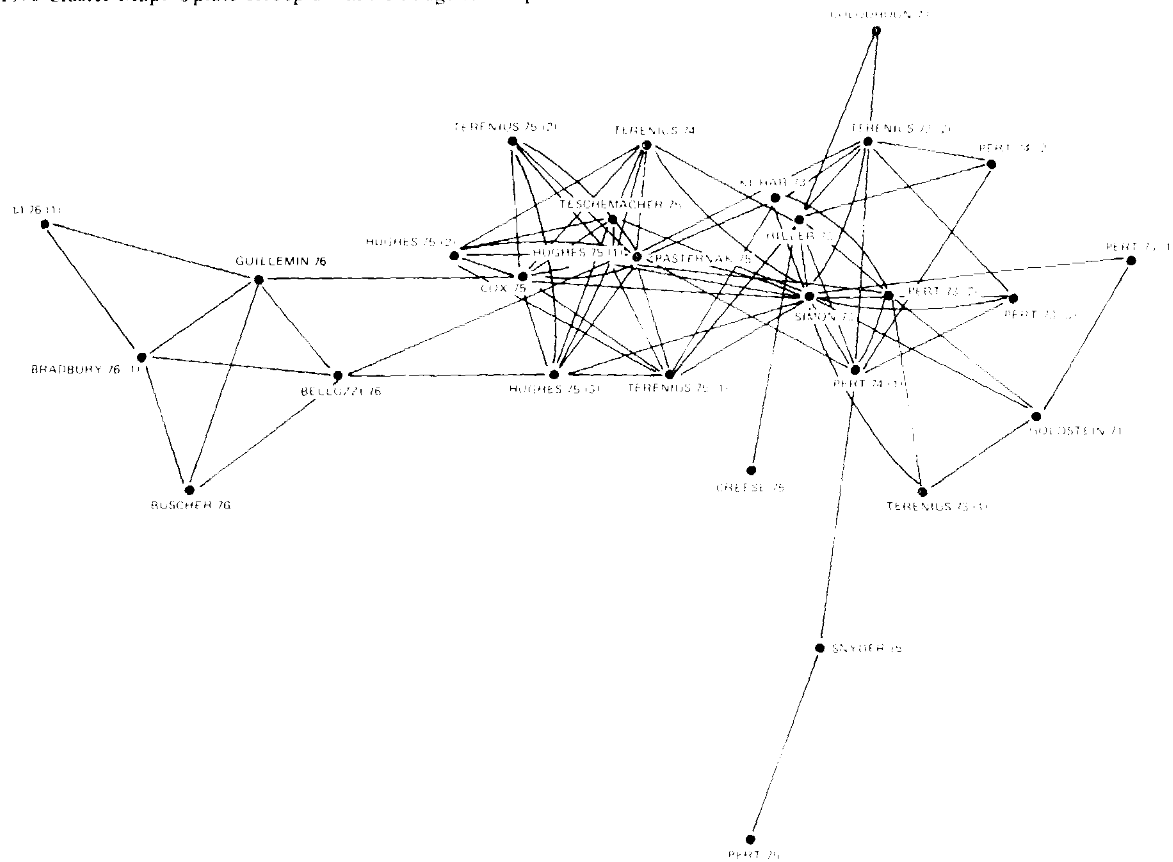
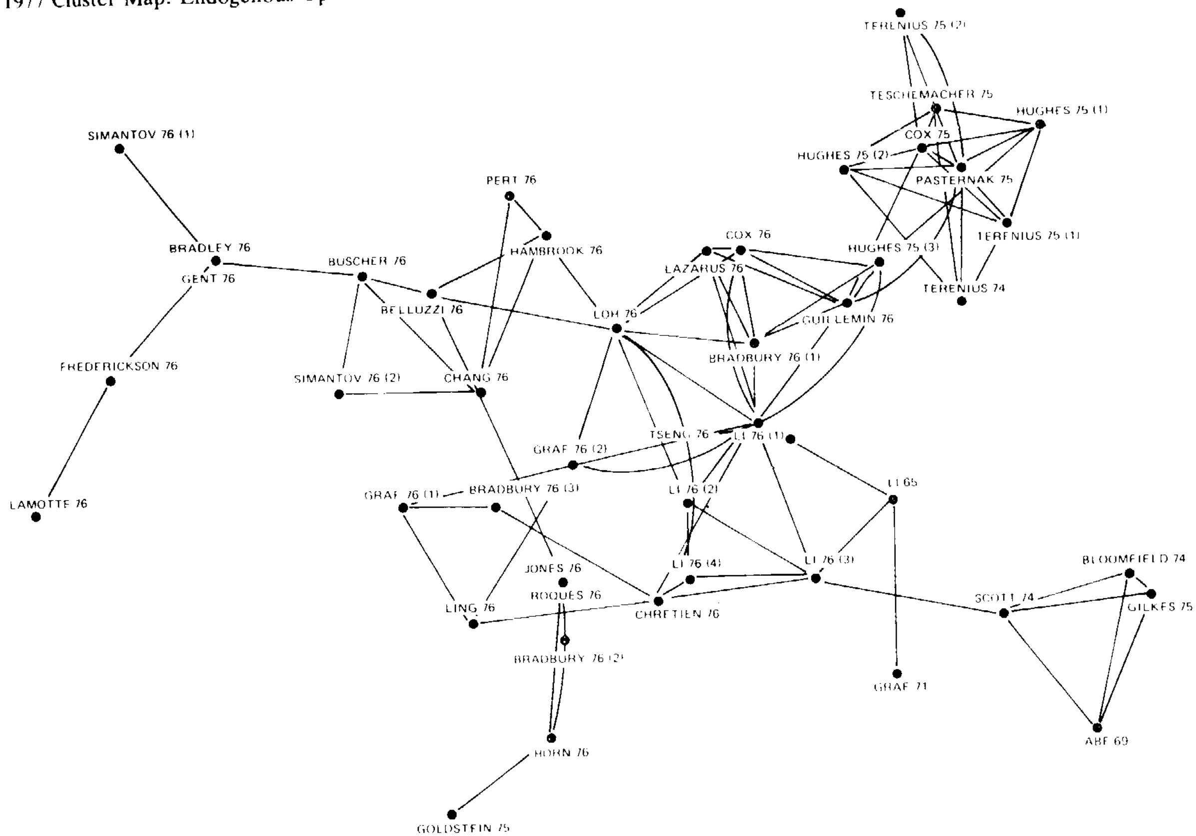


Figure 4. 1977 Cluster Map: Endogenous Opiates



Abe 69	**Abe K,** Nicholson W E, Liddle G W, Orth D N & Island D P. Normal and abnormal regulation of β-MSH in man. *J. Clin. Invest.* 48:1580-5, **1969**.
Belluzzi 76	**Belluzzi J D,** Grant N, Garsky V, Sarantakis D, Wise C D & Stein L. Analgesia induced *in vivo* by central administration of enkephalin in rat. *Nature* 260:625-6, **1976**.
Bloomfield 74	**Bloomfield G A,** Scott A P, Lowry P J, Gilkes J J H & Rees L H. A reappraisal of human β-MSH. *Nature* 252:492-3, **1974**.
Bradbury 76 (1)	**Bradbury A F,** Smyth D G & Snell C R. C fragment of lipotropin has a high affinity for brain opiate receptors. *Nature* 260:793-5, **1976**.
Bradbury 76(2)	**Bradbury A F,** Smyth D G & Snell C R. Biosynthetic origin and receptor conformation of methionine enkephalin. *Nature* 260:165-6, **1976**.
Bradbury 76(3)	**Bradbury A F,** Smyth D G & Snell C R. Lipotropin: precursor to two biologically active peptides. *Biochem. Biophys. Res. Commun.* 69:950-6, **1976**.
Bradley 76	**Bradley P B,** Briggs I, Gayton R J & Lambert L A. Effects of microiontophoretically applied methionine-enkephalin on single neurones in rat brainstem. *Nature* 261:425-6, **1976**.
Büscher 76	**Büscher H H,** Hill R C, Römer D, Cardinaux F, Closse A, Hauser D & Pless J. Evidence for analgesic activity of enkephalin in the mouse. *Nature* 261:423-5, **1976**.
Chang 76	**Chang J K,** Fong B T W, Pert A & Pert C B. Opiate receptor affinities and behavioral effects of enkephalin: structure-activity relationship of ten synthetic peptide analogues. *Life Sci.* 18:1473-81, **1976**.
Chrétien 76	**Chrétien M,** Benjannet S, Dragon N, Seidah N G & Lis M. Isolation of peptides with opiate activity from sheep and human pituitaries: relationship to beta-lipotropin. *Biochem. Biophys. Res. Commun.* 72:472-8, **1976**.
Collier 74	**Collier H O J** & Roy A C. Morphine-like drugs inhibit the stimulation by E prostaglandins of cyclic AMP formation by rat brain homogenate. *Nature* 248:24-7, **1974**.
Colquhoun 73	**Colquhoun D.** The relation between classical and cooperative models for drug action. *Drug Recept.* 1973:149-82, **1973**.
Cox 75	**Cox B M,** Opheim K E, Teschemacher H & Goldstein A. A peptide-like substance from pituitary that acts like morphine. 2. Purification and properties. *Life Sci.* 16:1777-82, **1975**.
Cox 76	**Cox B M,** Goldstein A & Choh H L. Opioid activity of a peptide, vβ-lipotropin-(61-91), derived from β-lipotropin. *Proc. Nat. Acad. Sci. US* 73:1821-3, **1976**.
Creese 75	**Creese I** & Snyder S H. Receptor binding and pharmacological activity of opiates in the guinea-pig intestine. *J. Pharmacol. Exp. Ther.* 194:205-19, **1975**.
Frederickson 76	**Frederickson R C A** & Norris F H. Enkephalin-induced depression of single neurons in brain areas with opiate receptors—antagonism by naloxone. *Science* 194:440-2, **1976**.
Gent 76	**Gent J P** & Wolstencroft J H. Effects of methionine-enkephalin and leucine-enkephalin compared with those of morphine on brainstem neurones in cat. *Nature* 261:426-7, **1976**.

Gilkes 75 **Gilkes J J H,** Bloomfield G A, Scott A P, Lowry P J, Ratcliffe J G, Landon J & Rees L H. Development and validation of a radioimmunoassay for peptides related to β-melanocyte-stimulating hormone in human plasma: the lipotropins. *J. Clin. Endocrinol. Metab.* 40:450-7, **1975.**

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Goldstein 74 **Goldstein A.** Opiate receptors. *Life Sci.* 14:615-23, **1974.**

Goldstein 75 **Goldstein A,** Goldstein J S & Cox B M. A synthetic peptide with morphine-like pharmacologic action. *Life Sci.* 17:1643-54, **1975.**

Gráf 71 **Gráf L,** Barát E, Cseh G & Sajgó M. Amino acid sequence of porcine β-lipotropic hormone. *Biochim. Biophys. Acta* 229:276-8, **1971.**

Gráf 76(1) **Gráf L,** Rónai A Z, Bajusz S, Cseh G & Székely J I. Opioid agonist activity of β-lipotropin fragments: a possible biological source of morphine-like substances in the pituitary. *FEBS Lett.* 64:181-4, **1976.**

Gráf 76(2) **Gráf L,** Székely J I, Rónai A Z, Dunai-Kovacs Z & Bajusz S. Comparative study on analgesic effect of Met^5-enkephalin and related lipotropin fragments. *Nature* 263:240-2, **1976.**

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Hiller 73 **Hiller J M,** Pearson J & Simon E J. Distribution of stereospecific binding of the potent narcotic analgesic etorphine in the human brain: predominance in the limbic system. *Res. Comm. Chem. Pathol. Pharmacol.* 6:1052-62, **1973.**

Horn 76 **Horn A S** & Rodgers J R. Structural and conformational relationships between the enkephalins and the opiates. *Nature* 260:795-7, **1976.**

Hughes 75(1) **Hughes J.** Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. *Brain Res.* 88:295-308, **1975.**

Hughes 75(2) **Hughes J,** Smith T, Morgan B & Fothergill L. Purification and properties of enkephalin—the possible endogenous ligand for the morphine receptor. *Life Sci.* 16:1753-8, **1975.**

Hughes 75(3) **Hughes J,** Smith T W, Kosterlitz H W, Fothergill L, Morgan B A & Morris H R. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 258:577-9, **1975.**

Jones 76 **Jones C R,** Gibbons W A & Garsky V. Proton magnetic resonance studies of conformation and flexibility of enkephalin peptides. *Nature* 262:779-82, **1976.**

Klee 74(1) **Klee W A** & Streaty R A. Narcotic receptor sites in morphine-dependent rats. *Nature* 248:61-3, **1974.**

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Kosterlitz 68 **Kosterlitz H W** & Watt A J. Kinetic parameters of narcotic agonists and antagonists, with particular reference to *N*-allylnoroxymorphone (naloxone). *Br. J. Pharmacol. Chemoth.* 33:266-76, **1968**.

Kuhar 73 **Kuhar M J**, Pert C B & Snyder S H. Regional distribution of opiate receptor binding in monkey and human brain. *Nature* 245:447-50, **1973**.

Lamotte 76 **Lamotte C**, Pert C B & Snyder S H. Opiate receptor binding in primate spinal cord: distribution and changes after dorsal root section. *Brain Res.* 112:407-12, **1976**.

Lazarus 76 **Lazarus L**, Ling N & Guillemin R. β-lipotropin as a prohormone for the morphinomimetic peptides endorphins and enkephalins. *Proc. Nat. Acad. Sci. US* 73:2156-9, **1976**.

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Li 76(1) **Li C H** & Chung D. Isolation and structure of an untriakontapeptide with opiate activity from camel pituitary glands. *Proc. Nat. Acad. Sci. US* 73:1145-8, **1976**.

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Li 76(4) **Li C H** & Chung D. Primary structure of human β-lipotropin. *Nature* 260:622-4, **1976**.

Ling 76 **Ling N** & Guillemin R. Morphinomimetic activity of synthetic fragments of β-lipotropin and analogs. *Proc. Nat. Acad. Sci. US* 73:3308-10, **1976**.

Loh 76 **Loh H H**, Tseng L F, Wei E & Li C H. β-endorphin is a potent analgesic agent. *Proc. Nat. Acad. Sci. US* 73:2895-8, **1976**.

Martin 67 **Martin W R.** Opioid antagonists. *Pharmacol. Rev.* 19:463-521, **1967**.

Pasternak 75 **Pasternak G W**, Goodman R & Snyder S H. An endogenous morphine-like factor in mammalian brain. *Life Sci.* 16:1765-9, **1975**.

Pert 73(1) **Pert C B** & Snyder S H. Properties of opiate-receptor binding in rat brain. *Proc. Nat. Acad. Sci. US* 70:2243-7, **1973**.

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Pert 73(3) **Pert C B**, Pasternak G & Snyder S H. Opiate agonists and antagonists discriminated by receptor binding in brain. *Science* 182:1359-61, **1973**.

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Pert 74(2) **Pert C B, Snowman A M & Snyder S H.** Localization of opiate receptor binding in synaptic membranes of rat brain. *Brain Res.* 70:184-8, **1974**.

Pert 75 — **Pert C B,** Kuhar M J & Snyder S H. Autoradiographic localization of the opiate receptor in rat brain. *Life Sci.* 16:1849-54, **1975**.

Pert 76 — **Pert C B,** Pert A, Chang J K, & Fong B T W. [D-Ala^2]-Met-enkephalinamide: a potent, long-lasting synthetic pentapeptide analgesic. *Science* 194:330-2, **1976**.

Roques 76 — **Roques B P,** Garbay-Jaureguiberry C, Oberlin R, Anteunis M & Lala A K. Conformation of Met^5-enkephalin determined by high field PMR spectroscopy. *Nature* 262:778-9, **1976**.

Scott 74 — **Scott A P** & Lowry P J. Adrenocorticotrophic and melanocyte-stimulating peptides in the human pituitary. *Biochem. J.* 139:593-602, **1974**.

Simantov 76(1) — **Simantov R,** Kuhar M J, Pasternak G W & Snyder S H. The regional distribution of a morphine-like factor enkephalin in monkey brain. *Brain Res.* 106:189-97, **1976**.

Simantov 76(2) — **Simantov R** & Snyder S H. Isolation and structure identification of a morphine-like peptide "enkephalin" in bovine brain. *Life Sci.* 18:781-8, 1976.

Simon 73 — **Simon E J,** Hiller J M & Edelman I. Stereospecific binding of the potent narcotic analgesic [^{3}H] etorphine to rat-brain homogenate. *Proc. Nat. Acad. Sci. US* 70:1947-9, **1973**.

Snyder 75 — **Snyder S H.** Opiate receptor in normal and drug altered brain function. *Nature* 257:185-9, **1975**.

Terenius 73(1) — **Terenius L.** Stereospecific interaction between narcotic analgesics and a synaptic plasma membrane fraction of rat cerebral cortex. *Acta Pharmacol. Toxicol.* 32:317-20, **1973**.

Terenius 73(2) — **Terenius L.** Characteristics of the "receptor" for narcotic analgesics in synaptic plasma membrane fraction from rat brain. *Acta Pharmacol. Toxicol.* 33:377-84, **1973**.

Terenius 74 — **Terenius L** & Wahlstrom A. Inhibitors of narcotic receptor binding in brain extracts and cerebrospinal fluid. *Acta Pharmacol. Toxicol.* 35:55, **1974.**

Terenius 75(1) — **Terenius L** & Wahlstrom A. Search for an endogenous ligand for the opiate receptor. *Acta Physiol. Scand.* 94:74-81, **1975**.

Terenius 75(2) — **Terenius L** & Wahlstrom A. Morphine-like ligand for opiate receptors in human CSF. *Life Sci.* 16:1759-64, **1975**.

Teschemacher 75 — **Teschemacher H,** Opheim K E, Cox B M & Goldstein A. A peptide-like substance from pituitary that acts like morphine. 1. Isolation. *Life Sci.* 16:1771-6, **1975**.

Tseng 76 — **Tseng L,** Loh H H & Li C H. β-endorphin as a potent analgesic by intravenous injection. *Nature* 263:239-40, **1976**.

simultaneously."[12] According to a story in *Science News*, Simon made the first oral presentation of the discovery, and Snyder and Pert published first.[2] Apparently Simon's announcement was made at a scientific meeting in April 1973, but the proceedings were never published. Yet, if we look at the papers themselves, we find that Terenius was the first to submit his article to a journal (November 6, 1972), beating Pert and Snyder by almost a month (December 1, 1972), and Simon's group by several (April 19, 1973). Therefore, each of these scientists has a strong claim on the discovery.

Candace Pert appeared on all three papers from Snyder's group—Pert 73(1), Pert 73(2), and Kuhar 73. She was first author of the paper announcing the discovery.

The 1974 cluster map and the articles themselves thus give important insights into the seminal research in this specialty. They also give us a list of four sure candidates for any award for opiate research: Goldstein, Snyder, Simon, and Terenius as the senior investigators. Among their team members, Pert also seems to be a contender, since she appeared on all Snyder's papers in the cluster map.

The 1975 cluster map reflects the increase of activity following the initial discovery. It shows a consolidation of work on opiate receptors. Other papers by Snyder and Pert (Pert 73(3)) and Simon's group (Hiller 73) appear. But most interesting is the paper at the right labeled Hughes 75. Its importance is suggested by the fact that it was cited enough times to appear in the 1975 cluster map the same year it was published. (It also appeared on our list of 1975 articles most-cited in 1975.[13]) In this paper Hughes announced the isolation of the compound he and Kosterlitz would later call enkephalin, an endogenous opiate-like substance which binds with opiate receptors.

This cluster map indicates that our list of candidates should also include Hughes and, by implication, his collaborator, Hans Kosterlitz. It also indicates that Pert should still be under consideration, for she consistently appears with Snyder.

The 1976 cluster map, more complex than the previous years', divides into three sections. At the right is an area which concerns opiate receptors. The central section is on endogenous opioid substances—enkephalin and endorphin, a second opioid substance isolated in 1975. The lefthand section deals with the isolation, structure, and analgesic effects of these substances.

From looking at the map and the original articles, we find that Hughes' discovery of enkephalins was not unique. The central portion of the cluster map also includes a paper by Terenius which independently announces the isolation of enkephalin. Again there seems to be an almost simultaneous discovery. If we look at the articles, we find that Hughes' paper was accepted by *Brain Research* on December 4, 1974. Terenius' paper was submitted a little more than a week later on December 13, 1974. Again, Terenius reinforces his candidacy with this discovery.

Goldstein also reinforces his candidacy. Two papers from his team (Teschemacher 75 and Cox 75) report the discovery of the second opioid substance: endorphin.

Pert continues to be the only coauthor of any of the senior investigators to appear so frequently in the clusters. Her papers dominate the righthand side of the map. Several have appeared in the earlier clusters, but two, labeled Pert 74(2) and Pert 75, are new. Both report even more precisely the location of opiate receptor binding in the brain.

The 1977 cluster map is still more diversified. Six sections are discernible here.

The upper right area (Terenius and Hughes papers) roughly corresponds to the central section of the 1976 cluster. It includes the early observations of endogenous opiate-like substances. To the left of this area is a group of papers focusing on one type of these substances, endorphin. Directly below it is a group of papers by Li, Graf, and others on the structure and amino acid sequence of these substances. In the lower right are papers discussing another brain hormone.

In the upper left, the papers generally deal with physiological effects of the opioid substances. Of prime importance here are the two papers (near the center of the cluster) which are labeled Chang 76 and Pert 76. Both articles were written after Pert had left Snyder's lab. They indicate that she is still a force within the specialty without the help of her mentor. The presence of these two papers confirms Pert's candidacy.

From this perusal of four clusters, it seems as though the Lasker Award Committee would have certainly been able to justify naming Goldstein, Simon, and Terenius, as well as the three researchers they recognized. In fact, these six did receive the National Institute of Drug Abuse's Pacesetter Research Award in 1977 for their work in the opiate area. If the jury was still concerned about graduate student Pert's contributions, they could have looked at more specific data on her work.

If we compare citation counts of the opiate receptor papers by Snyder and Pert with the citations to papers by Snyder and others, we find further evidence for the importance of Pert's contribution. From 1973 to 1976, Pert and Snyder co-authored 17 journal articles on opiate receptors. These papers have received to date an average of 87 citations per article. During the same period, Snyder and other collaborators published 23 papers in the opiate receptor field. These papers have received an average of 37.5 citations per article.

Of Snyder's papers on opiate receptors, Pert co-authored five of the six which received over 100 citations. She co-authored 10 of his 20 most-cited opiate receptor papers. None of Snyder's other co-authors has a citation record which can compare with Pert's.

Citation counts can also indicate that Pert's two post-Snyder papers in the 1977 cluster were not a flash in the pan. Since leaving Snyder's lab, she has published 18 articles (1975 to date). Seven of them appeared in 1978 and have had relatively little time to receive citations. Yet these 18 papers have received over 300 citations, or an average of about 16 citations per paper. And one of her 1976 papers proved to be among the 100 1976 papers most cited in 1976-1977.[14] Thus, Pert's work at NIMH continues to be significant to her colleagues. Although these data cannot prove that Pert made major contributions to the work she did with Snyder, they do indicate that she was *capable* of valuable contributions.

Both the cluster data and citation counts provide strong evidence that Candace Pert deserves formal recognition for her contributions.

With the addition of Pert to our list, we have identified seven scientists who could have appropriately shared the 1978 Lasker or National Institute of Drug Abuse (NIDA) awards. Some may object to naming such a large group. Since an award's prestige relies in part on exclusiveness, the argument runs, naming many co-winners each year may detract from the honor. (Nobels, for example, are limited to three co-winners per year. Lasker awards, however, have no formal limitations.) Certainly a large group of winners will decrease the financial rewards which go along with the honor. Yet justice may sometimes require a relatively large number of co-winners. The first obligation of an awards committee is to honor truly significant scientific research. If it is necessary to recognize the five, seven, or x number of researchers who made the important contributions, then so be it. Awards committees will have to face the reality of collaborative research, simultaneous discovery, and the increase in the number of scientists who may be worthy of sharing an honor.

ISI® would like to provide cluster maps to any awards committees that request them. I think committees will find them useful for getting an overview of an active research specialty and for indicating important articles in the area. To obtain cluster maps, members of awards committees may write to me at ISI, naming the specialties in which they are interested.

We may also publish cluster maps in the form of an *Atlas of Science*, as I suggested previously.[15] Let me repeat that cluster maps and other citation data should not be used alone. But in many cases, they can reveal simultaneous discoveries and identify researchers worthy of an award.

As we go to press, I would like to make note of a letter just published in *Science* and *Science News*. William Pollin of the NIDA wrote of the 1977 NIDA Pacesetter Research Award, which went to Goldstein, Hughes, Kosterlitz, Simon, Snyder, and Terenius: "In retrospect, we feel that it was a significant omission on our part that Dr. Candace Pert was not included. Her graduate student role was the issue at the time; subsequent increased awareness of her major contribution has led us to this revised conclusion."[16,17]

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A Note On Cluster Maps

Cluster maps are graphic displays of the cognitive structure of scientific research or knowledge. Cluster maps can be created at any level of specificity desired. Thus, a cluster map at the "macro" level can show the relationship between chemistry, physics, and medicine. At a more specific level we can show the relationship between various areas of the neurosciences. At a more "micro" level we can show the relationship between specific aspects of opiate receptors research.

Cluster maps are drawn by a purely algorithmic procedure using citation frequency data. ISI® creates cluster maps each year from citation data recorded in the annual *Science Citation Index® (SCI®)* and *Social Sciences Citation Index™ (SSCI™)*.

The first step is to identify all highly cited papers for a given year, such as those papers cited 15 times or more in 1978. Next, we determine how often any of these highly cited papers are cited together ("co-cited") in 1978. We then find the "level" of co-citation of each pair of co-cited papers (A & B):

$$\frac{\text{co-citations A \& B}}{\text{total citations A \& B} - \text{co-citations A \& B}}$$

The level of co-citation is an indication of the relatedness of the papers. The more often two papers are cited together, the stronger their relationship. We set a level of co-citation as a threshold and form the clusters (by a method called single-link clustering) of all papers co-cited above that threshold.

For each cluster there is a small group of these co-cited papers and a group of current citing papers. The titles of the *citing* papers help name the cluster. These names will change from year to year as knowledge within the field changes. In stable fields the co-cited works stay the same from year to year and the names change slightly. In fast-moving fields both may change rapidly. We use the technique of multidimensional scaling to position the papers on the cluster maps.

We have provided four annual cluster maps covering 1974 to 1977. Each map has been created from the corresponding annual *SCI*. Figure 1 is based on co-citation data from 59 citing papers. The level of co-citation (threshold) needed for papers to appear in the cluster was 10%. Six key papers, indicated by the first-author's name and year of publication, were co-cited above this threshold.

For Figure 2 we began with 141 citing papers. At a threshold of 11% co-citation, 16 heavily co-cited papers were identified for the cluster. However, only 10 of these are new. The other six appeared in the 1974 cluster.

Figure 3 is based on data from 278 citing papers. At the higher co-citation level of 18%, there are still 28 papers in the cluster. (Note how the clusters reflect, in their increasing complexity and number of co-cited papers, the growth of opiate research.)

For the 1977 cluster we began with 453 citing papers. With the level at 20%, there are 32 co-cited papers. Note that the six papers from the first cluster for 1974 have disappeared from the map. Keep in mind that these and other papers which have dropped off the map continue to be cited, but at a lower frequency.