

October 27, 1975

Number 43

Is memory contained in a chemical substance which can be transferred from one individual to another? It is a question whose answer may have enormous implications for education, for all fields of science, and for our entire society. Therefore, it seemed a worthwhile question with which to demonstrate how easy it is to use the Science Citation Index[®] (SCI[®]).

An hour's instruction is more than enough to make a competent SCI user out of an amateur--someone who's neither skilled in the use of indexes nor an expert in the subject area under investigation. Of course, for someone who *is* a subject specialist or an index sophisticate, using the SCI is even easier.

In order to illustrate the SCI's effectiveness in the hands of someone with no prior knowledge of chemical memory transfer, I asked A. E. Cawkell, ISI[®] 's Director of Research and Development to undertake an SCI search. His goal was to compile a bibliography on the subject.

Cawkell began his search with just two references, which were given to him by a specialist in the field. This was all he needed. The *SCI* provided the rest. Before discussing the results of Mr. Cawkell's search, it may be interesting to recall briefly the beginnings of the study of chemical transfer of memory.

In 1962, a fascinating and seminal paper was published by James V. McConnell of the University of Michigan.¹ In it. he describes his pioneering studies with planaria in 1953, when he began wondering what would happen if he "conditioned a flatworm, that cut it in two and let both halves regenerate. Which half would retain the memory?" He found that "the tails not only showed as much retention as did the heads, but in many cases did much better than the heads and showed absolutely no forgetting whatsoever. Obviously memory, in the flatworm, was being stored throughout the animal's body...."

In 1957, two groups of "worm runners"¹ hypothesized that memory could be transferred from a trained animal to an untrained one. They tried grafting the heads of trained flatworms onto the tails of untrained planaria. They tried grinding up the trained worms and injecting the pieces into the untrained worms. Finally, they decided to take advantage of the fact that under certain conditions, one flatworm will eat another. They conditioned a group of worms, chopped them into small pieces, and hand-fed the pieces to untrained "cannibal" worms.

They found that the cannibals which had eaten trained worms gave 50% more conditioned responses than a control group of cannibals which had eaten untrained worms. This demonstrated that a chemical substance being stored throughout the worms' bodies--probably **RNA**--was responsible for memory transfer.

In 1968, Ungar, Galvan and Clark,² working with rats, again demonstrated memory transfer. This time, however, the animals were trained to avoid the dark. When material extracted from the brains of trained rats was injected into untrained rats, the untrained animals also displayed fear of the dark.

The material responsible for this transfer of memory was dubbed scotophobin, from Greek skotos (darkness) and phobos (fear). It has since been found to lessen the time spent in the dark by rats, mice, goldfish, and roaches.³

Cawkell's SCI search produced an extensive bibliography and citation network for scotophobin-without the need to understand and assimilate the subject matter in each paper. The bibliography is reproduced on the following pages. Readers interested in the citation network diagrams can write to me.

It is enlightening to compare the performance of the SCI in this search with the expected performance of traditional indexes to the scientific literature. If Cawkell had used the largest biomedical index available he would *not* have found a heading for SCOTOPHOBIN--not in this year's index; not in any previous year. Not even a cross-reference.

In another traditional index one item from the bibliography was found in a rather unexpected place. The item was listed under DARK-NESS--an ironically appropriate heading.

Are there other chemical substances like scotophobin which contain the essence of memory and knowledge? Will some of these phobins, when ingested by humans, induce specific fears other than fear of the dark--such as fear of certain objects, symbols, words, or individuals? If *phobins* induce fear, are there also *philins* (to coin a term) which induce *preference*?

As always, scientific progress can lead to good or to evil. Along with the prospect of memory pills comes the prospect of a fiendishly effective love potion. We can only hope that probins are never used as weapons by the military, and that philins never fall into the hands of advertising agencies.

REFERENCES

1. McConnell J V. Memory transfer through cannibalism in planarians. Journal of Neuropsychiatry 3:42-48, 1962.

^{2.} Ungar G, Galvan L & Clark R H. Chemical transfer of learned fear. Nature 217:1259-61, 1968.

^{3.} Mitchell S R, Beaton J M & Bradley R J. Biochemical transfer of acquired information. International Review of Neurobiology 17:61-83, 1975.

SELECTED BIBLIOGRAPHY ON SCOTOPHOBIN AND 'MEMORY TRANSFER'

The items are arranged by year of publication, and within year by first author. This bibliography is 'selected' because it does not include all of the almost 200 articles identified in Mr. Cawkell's search. In Mr. Cawkell's words: "The references provided by Ungar and Stewart [items 50 and 48 in this list] were used as entry points into the *Citation Index*, and articles citing them were noted. A few of the more heavily cited articles were obtained, and the same process was repeated ("cycling") using their references as entry points. [In this cycling] a cut-off decision has to be made at some point beyond which it is considered that further searching would be unrewarding. The searcher has to make decisions about the branches to pursue, based on information acquired as the search proceeds, if he knows nothing at the outset... The searcher has to arbitrarily decide just what constitutes "the subject". In fringe areas, what should be listed and what should be omitted? For the non-subject expert these three limitations may be eased by reading a small number of key articles. (Putative key articles, which usually turn out to be *de facio* key articles, are the most heavily cited. These most cited articles are of course identified from the *SCI*.) From a perusal of portions of text keyed to specific references, a selection from the total number of retrieved articles was made...."

The bibliography which follows is that "selection." The effectiveness of this almost wholly algorithmic search technique can be evaluated by the reader. By chance, a review article, item 75 on this list, was being prepared at about the same time Mr. Cawkell made his search. In a last-minute updating of Mr. Cawkell's search in preparation of this editorial, that review article was retrieved. Readers may be interested in comparing this bibliography with that of the review by Mitchell *et al.*

- 1. Wilcoxon F. Individual comparisons by ranking methods. Biom. Bull. 1:80-3, 1945.
- 2. Mann H B & Whitney D R. On a test of whether one of two rnadom variables is stochastically larger than the other. Ann. Math. Statist. 18:50, 1947.
- 3. McConnell J V. Memory transfer through cannibalism in planarians. J. Neuropsychiatr. 3:42-8, 1962.
- Hartry A L, Keith-Lee P & Morton W D. Planaria-memory transfer through cannibalism re-examined. Science 146:274, 1964.
- Babich F R, Jacobson A L, Bubash S & Jacobson A. Transfer of a response to naive rats by injection of ribonucleic acid extracted from trained rats. Science 149:656, 1965.
- Fjeringstad E J, Nissen T & Roigaard-Peterson H H. Effect of ribonucleic acid (RNA) extracted from brain of trained animals on learning in rats. Scand. J. Psychol. 6:1, 1965.
- Gross C G & Carey F M. Transfer of learned response by RNA injection; failure of attempts to replicate. Science 150:1749, 1965.
- 8. Reinis S. Formation of conditioned reflexes in rats after parenteral administration of brain homogenates. Activitas Nervosa Superior 7:167, 1965.
- 9. Ungar G & Oceguera-Navarro C. Transfer of habituation by materials extracted from brain. Nature 207:301, 1965.
- Byrne W L, Samuel D, Bennett E L, Rosenzweig W R, Wasserman E, Wagner A R, Gardner F, Galambos R, Berber B D & Margules D L. Memory transfer. Science 153:658-59, 1966.
- 11. Essman W B & Lehrer G M. Is there a chemical transfer of training. Fed. Proc. 25:208, 1966.
- 12. Gordon M W, Deanin G G, Leonhardt H L & Gwynn R H. RNA and memory; a negative experiment. Amer. J. Psychiat. 122:1174-8, 1966
- 13. Luttges M A, Johnson T, Buck C, Holland J & McGauch J. An examination of transfer of learning by nucleic acid. Science 151:834-37, 1966.
- 14. Rosenblatt F, Farrow J T & Herblin W F. Transfer of conditioned responses from trained rats to untrained rats by means of a brain extract. Nature 209:46, 1966.
- 15. Rosenblatt F, Farrow J T & Rhine S. Transfer of learned behavior from trained to untrained rats by means of brain extracts. 1. Proc. Nat. Acad. Sci. USA 55:548-55, 1966.
- 16. Ungar G. Chemical transfer of learning; its stimulus specificity. Fed. Proc. 25:207, 1966.
- 17. Dyal J A, Golub A M & Marrone R L. Transfer effects of intraperitoneal injection of brain homogenates. Nature 214:720-21, 1967.
- 18. Essman W B & Lehrer G M. Facilitation of maze performance by RNA extracts from maze-trained rats. Fed. Proc. 26:263, 1967.

- 19. Gay R & Raphelson R. Transfer of learning by injection of brain RNA; a replication. Psychonom. Sci. 8:369-70, 1967.
- 20. Tirri R. Transfer of induced tolerance to morphine and promazine by brain homogenate. Experientia 23:268, 1967.
- 21. Ungar G & Irwin L N. Transfer of acquired information by brain extracts. Nature 214:453-5, 1967.
- Dyal J A & Golub A M. Further positive transfer effects obtained through injections of brain homogenates. Psychonom. Sci. 11:13, 1968.
- 23. Golub A M & McConnell J V. Transfer of response bias by injection of brain homogenates; a replication. Psychonom. Sci. 11:1, 1968.
- 24. Reinis S. Block of memory transfer by actinomycin D. Nature 220:177, 1968.
- Smits S E & Takemori A E. Lack of transfer of morphine tolerance by administration of rat cerebral homogenates. Proc. Soc. Exp. Biol. Med. 127:1167-71, 1968.
- Tunkl J. A. bibliography on chemical transfer of training in vertebrates. J. Biol. Psychol. 10:80-89, 1968.
- 27. Ungar G, Galvan L. & Clark R H. Chemical transfer of learned fear. Nature 217:1259-61, 1968.
- 28. Ungar G. Molecular mechanisms in learning. Perspect. Biol. Med. 11:217-32, 1968.
- 29. Fjerdingstad E J. Chemical transfer of learned preference. Nature 222:1079, 1969.
- 30. Ungar G. Chemical transfer of passive avoidance. Fed. Proc. 28:647, 1969.
- Ungar G & Galvan L. Conditions of transfer of morphine tolerance by brain extracts. Proc. Soc. Exp. Med. 130:287, 1969.
- 32. Wolthuis O L. Inter-animal information transfer by brain extracts. Arch. Internat. Pharmacodyn. 182:439-42, 1969.
- 33. Byrne W L (ed.). Molecular approaches to learning and memory. New York: Academic Press, 1970.
- 34. Frank B, Stein D G & Rosen J. Interanimal memory transfer; results from brain and liver homogenates. Science 169:399-402, 1970.
- Golub A M, Masiarz F R, Villars T & McConnell J V. Incubation effects in behavior induction in rats. Science 168:392, 1970.
- Hutt L D & Elliott L. Chemical transfer of learned fear; failure to replicate Ungar. Psychonom. Sci. 18:57, 1970.
- Ungar G. Molecular mechanisms in information processing. Internat. Rev. Neurobiol. 13:223-25, 1970.
- Ungar G (ed.). Molecular mechanisms in memory and learning. New York: Plenum, 1970.
- Malin D H, Bolub A M & McConnell J V. Effect of an RNA-rich extract on acquisition of a one-way avoidance response in rats. Nature 233:211, 1971.
- Goldstein A, Sheehan P & Goldstein J. Unsuccessful attempts to transfer morphine tolerance and passive avoidance by brain extracts. Nature 233:126-29, 1971.
- Guttman H N & Gronke L. Passive transfer of learned dark and step-down avoidance. Psychonom. Sci. 24:107-09, 1971.
- 42. Braud L W & Braud W G. Biochemical transfer of relational responding (transposition). Science 176:522, 1972.
- 43. Bryant R C, Golub A M, McConnell J V & Rosenblatt F. Non-specific behavioral effects of substances from mammalian brain. Science 178:521-22, 1972.
- 44. Bryant R C, Santos N N & Byrne W L. Synthetic scotophobin in goldfish; specificity and effect on learning. Science 177:635-36, 1972.
- 45. Guttman H N, Matwyshyn G & Warriner G H. Synthetic scotophobin-mediated passive transfer of dark avoidance. Nature Biol. 235:26-27, 1972.
- Malin D H & Guttman H N. Synthetic rat scotophobin induces dark avoidance in mice. Science 178:1219-20, 1972.
- 47. Stein D G & Rosen J J. Non-specific behavioral effects of substances from mammalian brain. Science 178:522, 1972.
- 48. Stewart W W. Comments on the chemistry of scotophobin. Nature 238: 202-20, 1972.
- 49. Ungar G. Molecular coding of information in the nervous system. Naturwissenschaften 59:85, 1972.

- 50. Ungar G, Desiderio D M & Parr W. Isolation, identification and synthesis of a specific-behavior-inducing brain peptide. Nature 238:198-202, 1972.
- Braud L W & Braud W G. Re-examination of biochemical transfer of relational learning; reply. Science 179:305, 1973.
- 52. Braud W G & Hoffman R B. Response facilitation and response inhibition produced by intracranial injections of brain extracts from trained donor goldfish. *Physiol. Psychol.* 1:169, 1973.
- 53. Bryant R C. Studies of activity of learning-linked rat peptide scotophobin in common goldfish, Carassius auratus. Tex. Reports. Biol. & Med. 31:557, 1973.
- Corwin T M & Stanford A L. Increased susceptibility to audiogenic-seizure resulting from injection of brain extract from acoustically primed mice. *Physiol. Psychol.* 1:324-26, 1973.
- 55. Goldstein A. Comments on isolation, identification and synthesis of a specificbehavior-inducing brain peptide. Nature 242:60-62, 1973.
- 56. Goldstein A. Correction. Nature 242:544, 1973.
- 57. Vieira F J A, Weyne M E, Oliveira L M, Gondim F A L & Casimiro A R. Induction (transfer) of an operant-behavior by injection of brain extract. *Psychopharmacologia* 33:339-48, 1973.
- Wied D D, Sarantakis D & Weinstein B. Behavioral evaluation of peptides related to scotophobin. Neuropharmacology 12:1109-15, 1973.
- 59. Yaremko R M & Hill W A. Re-examination of biochemical transfer of relational learning. Science 179:305, 1973.
- 60. Bisping R, Bentz U, Boxer P & Longo N. Chemical-transfer of learned color discrimination in goldfish. Nature 249: 771-72, 1974.
- 61. Dressler D & Rosenfeld S. Chemical nature of transfer factor. Proc. Nat. Acad. Sci. USA. 71:4429-34, 1974.
- 62. Lackner H & Tieman N. Synthesis of hexapeptide acting physiological behavior. Naturwissenschaften 61:217-18, 1974.
- 63. Malin D H. Synthetic scotophobin; analysis of behavioral-effects on mice. Pharmacol. Biochem. & Behav. 2:147-53, 1974.
- 64. Modigliari V. & Seamon J G. Transfer of information from short-term to long-term memory. J. Exper. Psychol. 102:768-72, 1974.
- 65. Radcliff G J & Shelton J W. Molecular coding of maze learning; demonstration by bioassay. Experientia 30:1284-86, 1974.
- Parr W & Holzer G. Synthesis of C-terminal octapeptide having sequence proposed for scotophobin. Ann. Chemie. 6:982-89, 1974.
- Parr W & Holzer G. Synthesis of C-terminal octapeptide having sequence proposed for scotophobin. Ann. Chemie, 1974:982-89, 1974.
- 68. Smith L T. Interanimal transfer phenomenon; Review. Psychol. Bull. 81:1078-95, 1974.
- 69. Ungar G. Molecular coding of memory. Life Sciences 14:595-604, 1974.
- 70. Ungar G. Peptides and memory. Biochem. Pharm. 23:1553-58, 1974.
- 71. Webster J C & Fox K A. Altered learning by recipients of brain extracts from trained and retrained donors. Pharmacol. Biochem. & Behav. 2:209-13, 1974.
- 72. Guttman H N & Cooper R S. Oligopeptide control of step-down avoidance. Life Sciences 16:915-23, 1975.
- 73. Guttman H N, Weinstein B, Bartschot R M & Tam P S. Reputed rat scotophobin prepared by a solid-phase procedure shown invalid by comparison with a product derived from a classical synthesis on basis of physical and biological properties. Experientia 31:285-88, 1975.
- Kaplan B B & Sirlin J L. Macromolecules and behavior. 2. Training-induced alteration in leucine transfer-RNA of goldfish brain. Brain Research 83:451-68, 1975.
- 75. Mitchell S R, Beaton J M & Bradley R J. Biochemical transfer of acquired information. Internat. Rev. Neurobiol. 17:61-83, 1975.
- 76. Ungar G. Peptides and behavior. Internat. Rev. Neurobiol, 17:37-60, 1975.