COMPLEMENT IN THE PATHOPHYSIOLOGY OF HUMAN DISEASE

To the Editor: In his review in the June 11 issue,[1] Dr. Frank presents a list of inherited deficiencies of complement and complement-related proteins. To the best of our knowledge, that list is incomplete, since it fails to mention a protein recently described by us.[2,3] It is a 40,000-dalton protein, found in synovial and serosal fluids, with the ability to inactivate the chemotactic activity of the complement-derived peptide C5a.

This inhibitor is specific against C5a, since it does not inactivate the chemotactic activity of F-met-leu-phe and does not affect the cells themselves. It is released by fibroblasts originating from synovial and peritoneal tissues and is not released by skin fibroblasts.[4] The C5a inhibitory activity was found to be within normal limits in all synovial and peritoneal fluids studied. However, it was deficient in synovial[5] and peritoneal[6] fluids of patients with familial Mediterranean fever. We believe that this C5a inhibitor has a role in the regulation of inflammation in synovial and serosal tissues and that its deficiency in familial Mediterranean fever may explain, at least in part, the attacks of sterile inflammation characteristic of this disease.

Mount Scopus, Jerusalem, Israel 91240

YAACOV MATZNER, M.D.
Hadassah University Hospital

1. Frank MM. Complement in the pathophysiology of human disease. N Engl J Med 1987; 316:1525-30.
2. Matzner Y, Partridge REH, Babior BM. A chemotactic inhibitor in synovial fluid. Immunology 1983; 49:131-8.
3. Matzner Y, Brzezinski A. A C5a inhibitor in peritoneal fluid. J Lab Clin Med 1984; 103:227-35.
4. Matzner Y, Gavison R, Shlomai Z. Production of C5a antagonist by synovial and peritoneal tissue fibroblasts. J Cell Physiol 1986; 129:215-20.
5. Matzner Y, Partridge REH, Levy M, Babior BM. Diminished activity of a chemotactic inhibitor in synovial fluids from patients with familial Mediterranean fever. Blood 1984; 63:629-33.
6. Matzner Y, Brzezinski A. C5-a inhibitor deficiency in peritoneal fluids from patients with familial Mediterranean fever. N Engl J Med 1984; 311:287-90.

The above letter was referred to Dr. Frank, who offers the following reply:

To the Editor: Restrictions on the length of our review made it impossible to be exhaustive. We did not mention many important areas of complement research in the interest of simplicity and clarity. Dr. Matzner has published a series of papers describing a C5a inhibitor that is absent in synovial and peritoneal fluids from patients with familial Mediterranean fever. To my knowledge the work has not yet been confirmed by another group, and I elected not to include it in my review. It is potentially quite important. It will be interesting to see how information in this area develops.

MICHAEL M. FRANK, M.D.
National Institute of Allergy and Infectious Diseases
Bethesda, MD 20892

EAR-CLICKING "TINNITUS" RESPONDING TO CARBAMAZEPINE

To the Editor: This is to report the experience of a 43-year-old male pediatric cardiologist (me) with a most annoying ear clicking, a form of tinnitus, which greatly affected my professional work and puzzled several authorities. This problem responded to treatment with carbamazepine after two middle-ear operations had failed to provide relief.

For three years I had a clicking sensation in my right ear that was triggered by inner and outer sounds, even ambient noise. Neurologic, audiologic, and otolaryngologic examinations were unrevealing. On the assumption that the condition was due to a myoclonus in the middle ear, muscle relaxants were tried unsuccessfully.

Tympanometric evaluation of the right ear, eustachian-tube function during an episode of clicking, and an electroencephalogram were all normal. Computed tomography of the petrous bone, brain stem, and cerebellopontine angle revealed no abnormalities.

Speech sounds at 65 dB were sufficient to initiate the clicking tinnitus. No tinnitus was initiated by contralateral stimulation. Use of a tinnitus masker with a band of noise centered at 4000 Hz did not relieve the clicking tinnitus or prevent its occurrence.

Surgical release of the stapedial tendon worsened the condition. Release of the tensor muscle of the tympanum provided no relief.

On the assumption that the clicking could be central neurologic or perceptive in origin, a trial with carbamazepine was initiated because of the well-known relief of trigeminal neuralgia provided by this drug, in the hope of a similar effect on dysesthesia of the acoustic nerve. At a dose of 200 mg three times daily, which produced a plasma level of 11.8 ng per milliliter, there was almost complete relief. Initially, the tinnitus returned fully when the drug was discontinued for more than 24 hours. The favorable response returned with resumption of treatment.

After 45 days of therapy and because of liver toxicity, the medication was stopped. At about 35 days after cessation of the carbamazepine, the tinnitus recurred, first at a low level and then gradually increasing to range from 20 to 70 percent of its original level. A caffeine-free diet was of slight help. However, resumption of carbamazepine produced an excellent effect.

Neurologists and otolaryngologists should be aware of this condition, because medical treatment with carbamazepine and a caffeine-free diet can be of great help. Carbamazepine can be given for a prolonged period whenever the patient has symptoms, with adjustment of the dose according to the status of liver function.

MOHAMED K. MARDINI, M.D.
Fairfax Hospital
Falls Church, VA 22046

INCIDENCE OF RECREATIONAL USE OF 3,4-METHYLENEDIMETHOXYMETHAMPHETAMINE (MDMA, "ECSTASY") ON AN UNDERGRADUATE CAMPUS

To the Editor: 3,4-Methylenedimethoxymethamphetamine (MDMA, "ecstasy") is a ring-substituted amphetamine derivative that is chemically related to both hallucinogens and stimulants. In the 1970s and early 1980s, the drug gained popularity as an adjunct to psychotherapy.[1-3] The drug has been reported to induce a state of euphoria and enhanced self-awareness without psychotic effects or visual distortions.[4] However, because of reports that MDMA and other related compounds had neurotoxic effects in laboratory animals,[5-9] the drug was placed on Schedule I by the Food and Drug Administration in July 1985.

However, undocumented reports have suggested that the recreational use of MDMA has been increasing at certain undergraduate campuses in the United States during the past few years. The present study attempted to determine the incidence of use of this compound at a university campus. Undergraduates at Stanford University were randomly and anonymously polled about the possible use of MDMA. The subjects were asked whether they had ever taken "ecstasy" or "MDMA." Of a total of 369 subjects interviewed, 143 (39 percent) reported that they had used the drug at least once. The frequency of use by the subjects ranged from 1 to 38 times. The median number was 4, and the mean was 5.4. The amount of drug taken in a single dose ranged from 60 to 250 mg (approximately 1 to 4 mg per kilogram of body weight).

The principal finding of the present study was that 39 percent of randomly selected undergraduate students at a major university reported having taken MDMA for recreational use — documentation of extensive recreational use of this agent. The increasing popularity of this Schedule I compound is important because of its neurotoxic effects in laboratory animals[5-9] and the human deaths attributed to its recreational use.[10] To date, there is no evidence to suggest that MDMA is neurotoxic in humans. However, the extensive recreational use of this compound by certain populations

should allow the accurate determination of its long-term effects on the human nervous system in the years ahead.

STEPHEN J. PEROUTKA, M.D., PH.D.
Stanford University
Stanford, CA 94305 School of Medicine

1. Shulgin AT. The background and chemistry of MDMA. J Psychoactive Drugs 1986; 18:291-304.
2. Greer G, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs 1986; 18:319-27.
3. Downing J. The psychological and physiological effects of MDMA on normal volunteers. J Psychoactive Drugs 1986; 18:335-40.
4. Snyder SH. Drugs and the brain. New York: W.H. Freeman, 1986:179-205.
5. Ricaurte G, Bryan G, Strauss L, Seiden L, Schuster C. Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. Science 1985; 229:986-8.
6. Schmidt CJ, Wu L, Lovenberg W. Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analog. Eur J Pharmacol 1986; 124: 175-8.
7. Stone DM, Stahl DC, Hanson GR, Gibb JW. The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) on monoaminergic systems in the rat brain. Eur J Pharmacol 1986; 128:41-8.
8. Schmidt CJ. Neurotoxicity of the psychedelic amphetamine methylenedioxymethamphetamine. J Pharmacol Exp Ther 1987; 240:1-7.
9. Commins DL, Vosmer G, Virus RM, Woolverton WL, Schuster CR, Seiden LS. Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. J Pharmacol Exp Ther 1987; 241:338-45.
10. Dowling GP, McDonough ET III, Bost RO. 'Eve' and 'Ecstasy': a report of five deaths associated with the use of MDEA and MDMA. JAMA 1987; 257:1615-7.

BOOK REVIEWS

PEDIATRICS

Eighteenth edition. Edited by Abraham M. Rudolph, Julien I.E. Hoffman, and Susan Axelrod. 1919 pp., illustrated. East Norwalk, Conn., Appleton and Lange, 1987. $85.

RUDOLPH'S PEDIATRICS: A STUDY GUIDE

Edited by Robert H. Pantell, David A. Bergman, Maureen T. Shannon, and Benjamin W. Goodman, Jr. 266 pp., illustrated. East Norwalk, Conn., Appleton and Lange, 1987. $29.95.

The first of these two books, *Pediatrics*, is a highly respected textbook that has a long and distinguished history beginning before the end of the past century, when it was Holt's *Diseases in Infancy and Childhood* (1897). Although such names as Howland and Barnett have appeared on the cover as editors of subsequent editions, Rudolph has edited this book since its 16th edition (1977). Despite its status as a classic, this book remains in an unrelenting struggle with its arch-rival classic, Nelson's *Textbook of Pediatrics*, for "most favored" status among the textbooks used by practitioners, residents, and students in pediatrics. Advocating one of these two textbooks over the other often involves a degree of religious fervor.

This 18th edition has undergone considerable modification while retaining a structure and quality reminiscent of previous editions. A comprehensive review of pediatrics is presented in an easily readable style. The presentation has better spacing and highlighting, enhancing its usefulness and legibility. The liberal use of tables and illustrations, many of which are new to this edition, prevents the text from becoming dull and ponderous. The list of tables included after the table of contents is a new and timesaving aid for readers trying to review (or remember) a specific topic. The table of contents itself has been given a fresh look, with individual subsections enumerated for easy reference.

Most (but not all) sections begin, as the editors promise in the preface, with a helpful discussion of basic physiology or embryology. A paucity of such information in the sections on oncology and on gastrointestinal diseases is a glaring exception. The book is generally quite up to date, with many references to sources published in the mid-1980s. The discussions of therapy for Kawasaki's disease and of interventional cardiology are impressively current. Welcome changes since the 17th edition include an expanded section on childhood development, with many helpful summary tables, a thorough discussion of fetal growth and development, a primer on molecular genetics, and a beautifully designed summary table of syndromes of multiple congenital anomalies. The revised section on fluid and electrolyte physiology is shorter and does not contain the practical advice and case studies of the earlier edition. This is unfortunate, since fluid and electrolyte physiology is such an integral part of pediatrics.

My principal frustration with the previous edition — the often awkward topic placement and incomplete indexing — remains unaltered in regard to this edition. Such neonatal conditions as jaundice, anemia, and hydrops are not discussed comprehensively in (or indexed under) the section on the neonate, but must be sought in chapters on the gastrointestinal tract and blood. The (somewhat brief) section on cystic fibrosis is found in the chapter on the lung, whereas diabetes mellitus and hypoglycemia are discussed in the "genetics" chapter. This sometimes inconsistent and illogical organization results in inefficiency and some redundancy. The index in this edition is 25 pages shorter than that in the previous edition (and that in the Nelson book). The headings under "asthma" contain only 7 listings for two separate discussions of the same topic, in contrast to 47 listings for one major discussion of asthma in Nelson's competing textbook.

How does this edition of *Pediatrics* hold up in a comparison with the 13th edition of the Nelson book (which also has a 1987 copyright date)? Quite well, on balance, the foregoing criticisms notwithstanding. Each book has its advantages and shortcomings, but both are easily readable, current works. This edition of Rudolph's book sometimes fails to cover basic introductory material that is nicely discussed in Nelson's book. For example, although the section on neurologic disease contains a review of the basic laboratory techniques used in the discipline, there is no similar discussion of the techniques employed in evaluating pulmonary dysfunction. The discussion of the acquired immunodeficiency syndrome in Rudolph's book is welcome and more comprehensive than that in Nelson's, but the helpful commentary on adolescent homosexuality in the Nelson book is notably absent in the Rudolph book. The discussions of medical ethics and of the transmission of certain drugs in breast milk are better presented by Rudolph, but his book contains little practical advice regarding such important issues as the difficulties encountered by mothers who are breast-feeding, the risk factors for neoplasia to which a pediatrician should be alerted, and the guidelines for determining when to refer patients for liver transplantation. Such commentary would have complemented the more "factual" information in the book.

The second book here, the study guide to the Rudolph book, contains a series of multiple-choice questions on each chapter, and may be useful for medical students or residents who wish to pay its $30 price.

This latest edition of *Pediatrics* is definitely an improvement over its predecessor. This book or Nelson's book belongs in the library of any physician caring for children. Most of the material in the two books is identical. If there is any notable difference between the two, it is that Nelson's is more "user friendly."

ROBERT J. WINTER, M.D.
Chicago, IL 60611 Northwestern University Medical School

PRIMARY PEDIATRIC CARE

Edited by Robert A. Hoekelman, Saul Blatman, Stanford B. Friedman, Nicholas M. Nelson, and Henry M. Seidel. 1776 pp., illustrated. St. Louis, C.V. Mosby, 1987. $65.

This comprehensive textbook on pediatrics has been developed for primary health care practitioners. No less than 220 distinguished authors have provided a wealth of carefully edited, first-rate information.