

ASP NEWSLETTER

Volume 25, Number 1

Winter, 1989

HEINZ G. FLOSS 1988 RECIPIENT OF ASP RESEARCH AWARD

Heinz G. Floss, Professor of Chemistry at the University of Washington in Seattle, was awarded the 1988 Research Award in Natural Products from the American Society of Pharmacognosy at the International Research Congress on Natural Products in Park City, Utah in July, 1988

Floss is internationally known for his work on the biosynthesis of natural products. He has worked on the biosynthesis of microbial metabolites, of ergot alkaloids, and of riboflavin, among others, and his work has often led to unusual findings. His work on riboflavin, for example, revealed completely unexpected chemistry for the derivation of the skeleton and of the ribitol side-chain.

Colleagues have described his work as "esthetically pleasing, intellectually satisfying, and extremely successful" and as "quite beautiful". He has received numerous other awards and honors, including the Research Achievement Award in Natural Products of the Academy of Pharmaceutical Sciences and an honorary D.Sc. degree from Purdue University.

Floss was born August 28, 1934 in Berlin, West Germany. He obtained a Vordiplom (BS) in Chemistry from Technische Universitat, Berlin, in 1956, and the Dr. rer. nat. in organic chemistry from Technische Universitat, Munich, under Prof. Dr. F. Weygard in 1961. He served as Associate Professor and Professor of Medicinal

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PRESIDENT SHIMIZU ADDRESSES 1988 ANNUAL MEETING

It was a great honor for me to have served as President of the Society particularly at the time when both the number of membership and the reputation of the Society among the scientific community were steeply upward. While we are euphoric about this upswing, we also have to look closely at hard facts and give some thought about the future of the Society.

Once pharmacognosy was an important subject in pharmacy education, but it is now almost at its extinction giving a way to all clinical pharmacy. In some schools, it barely exists only as a portion of medicinal chemistry or other subjects. How many pharmacy schools still maintain pharmacognosy departments? The name may not be so important after all, but it is sad to see the discipline itself including research is so lightly considered by the administrators that even some of the programs which distinguished produced many scientists, have been pushed to non-entity. This is ironical in view of the fact that more and more recognitions have been given to pharmacognosy or natural products study by the people outside of pharmacy schools ... as reflected in the statistics of the aforementioned surge. The recognitions partly come from the realization that pharmacognosy - the study of natural drugs - is thriving in such countries as Japan, China, and European countries. In those countries, the reevaluation of traditional drugs and natural products

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ASP SURVIVING CHARTER MEMBERS LISTED

The year 1989 will mark the end of a decade of unprecedented scientific and technologic development. reflective retrospection on our Society is appropriate. The American Society of Pharmacognosy was voted into existence in Chicago on a very hot August 10, 1959, at the business meeting of the 36th annual meeting of the Plant Science Seminar. Chairman Edson F. Woodward of the Plant Science Seminar recognized Norman R. Farnsworth, Chairman of the Constitution and By-Laws Committee (Jack L. Beal and Egil Ramstad members), who made the "birthing" motion; it passed unanimously.

Secretarial archives reveal that the Society began its organizational life with 136 Charter Members; they paid \$5.00 for their initial year's dues. A review of the Charter Membership List and reflection on the intervening years reveal that most of the old-timers are gone and that the young Turks have aged. The latter is readily apparent to everyone who has attended a recent meeting; the albino (maturity-onset leukotrichia) Varro E. Tyler and the cigarless (surgically removed) Norman R. Farnsworth are ersatz images of the Society's first two Presidents.

Twenty-five of the Charter Members, including 13 Past Presidents, are still active in the Society. They initially comprised 18.4% of the Society, but growth has diluted this resource to 5.6% of the current membership.

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FLOSS - Continued from Page 1, Column 1.

Chemistry at Purdue University from 1966-1982, and as Professor of Chemistry and Chairman at the Ohio State University from 1982-1987, before taking up his present position at the University of Washington.
Congratulations Dr. Floss!

CHARTER MEMBERS - Continued from Page 1, Column 3.

Charter members who are also on the current membership list are:

Jack L Beal (President 1962-63)
Ralph Blomster (President 1972-73)
Lynn R. Brady (President 1970-71)
John K. Brown
David P. Carew (President 1965-66)
Philip Catalfomo (President 1975-76)
Franklin R. Cole
Norman R. Farnsworth (President 19611962)

Noel M. Ferguson Harry H.S. Fong (President 1978-79) Melvin R. Gibson (President 1964-65) Carl H. Johnson John D. Leary Esteban Nunez-Melendez Ara G. Paul Joseph Schradie Lee C. Schramm Arthur E. Schwarting E. John Staba (President 1971-72) Elmore H. Taylor (President 1968-69) Varro E. Tyler (President 1959-61) Rolf Westby

Jack K. Wier (President 1980-81) Charles L. Winek

Heber W. Youngken, Jr. (President 1969-70)

Reported from the record by Lynn Brady

SHIMIZU - Continued from Page 1, Column 2.

as therapeutic agents has been actively conducted.

This year, for the first time, we have a joint meeting with the Japanese Society of Pharmacognosy. Japanese word for pharmacognosy if "shoyaku-gaku", which literally means the study of raw or live drugs. It should be noted that, in Japan, traditional crude drugs are qualified for the third-party payments, and hundreds of different regimens are prescribed by doctors in large reputable hospitals. At the same time, teams of pharmacognosists, chemists, pharmacologists, and medical doctors are actively studying the plant extracts under the light of modern science. Our friends in Japanese pharmacy schools have been enjoying a tremendous reputation among world scientific communities. In Europe, though not as much as in Japan, crude drugs still have their position. We often hear stories from surprised students who became ill during their trips to Europe and were given galenical preparations by doctors. Unfortunately, in the United States, lack of interest in natural drugs by the mainstream medical, pharmacy community has pushed these potential natural healers to a back room - the dangerous realm of non-science or superstition. False or exaggerated claims of efficacy is not uncommon for herbs and "crude drugs" sold by popular health-food stores. This is a very unfortunate situation.

Our medical community, - clinicians, especially - seem to forget the very fact that many of the important drugs they use are some way derived from natural sources, and many of them from traditional drugs. Without those natural drugs or leads from them, topics which our clinical pharmacists like to talk about would never have existed and thus there would be no jobs for them! It is dangerous to build a profession solely on applications. The strength and reputation of a profession come from its wide and solid base. Imagine medical schools abandoning basic biomedical components!

Recently we often hear of the loss of American competitive strength in business with foreign countries. A similar thing may happen in the pharmacy area. The negligence of basics in both research and education would lead to serious consequences in the future. The study of natural products is very complex and tedious. People do not realize that it takes many years of experience and tradition for one to be an able researcher. Already, among international pharmaceutical companies, there has been an acute realization that the U.S. can not provide good human resources to carry out natural products research, and they are not hesitant to move some of their operations to such countries as Japan.

The American Chemistry community is also not innocent on this issue. Traditionally, synthesis and reaction studies have been over-emphasized, and much less credit has been given to the first-order natural products research. The total synthesis of a fancy molecule or discovery of a new reaction is still the quickest way for a young chemist to attain national fame.

It is my sincere hope that the American Society of Pharmacognosy will provide an ideal ground where all scientists who are interested in natural products can meet, discuss, and help each other. We have to constantly struggle to upgrade the quality of the science we practice. Our journal, which is our show window, has to publish only first-class papers. We have to relate our problems to the main stream of biology, pharmacology, and biochemistry. We should promote the education of young successors. We should recognize our fellow scientists' accomplishments. Collaborations with foreign scientists are also very important to open our eyes to what is going on outside of the United States. The Society has already taken several steps to these goals, but actual progress is due to efforts of individual members.

SOCIETY NEWS

H.H. Mathur Retires

After 18 years of service to the Indian Institute of Technology in Bombay, India, H.H. Mathur has retired. Dr. Mathur has since joined Bhavnagar University as Professor of Chemistry responsible for the organization of the new Department of Marine Science.

Best wishes, Dr. Mathur!

FUTURE MEETINGS

Future ASP Meetings

1989 - August 6-10 University of Puerto Rico MORE DETAILS IN NEXT ISSUE

1990 - July 17-22 Joint meeting with the Gesellschaft Fur Arzneipflanzenforschung, University of Bonn, West Germany.

1991 - University of Chicago 1992 - Washington - Baltimore

American Association of Pharmaceutical Scientists Future Meetings

Fourth Annual Meeting, October 22-27, 1989, Atlanta, Georgia.

Phytochemical Society of Europe Future Meetings

Biochemistry and Molecular Biology of Plant-Pathogen Interactions to be held at University of East Anglia, Norwich, U.K. in April, 1989. For details contact: Dr. P.M. Mullineaux, Department of Virus Research, John Innes Institute, Colney Lane, Norwich NR4 7UH, U.K.

Other Meetings of Interest

International Congress for the History of Pharmacy to be held in Athens, Greece, April 15-18, 1989. For further information contact: 1989 International Congress for the History of Pharmacy, c/o EASY TRAVEL, 19, Anagnostopoulou Street, GR-106 73 Athens, Greece. Telex: 223589 EASY GR.

Caribbean-Europe Health Ethnopharmacological Seminar, Martinique, April 16-19, 1989. For information contact: Chambre de Commerce et D'Industrie de la Martinique, Cellule RCE, B.P. 478, 97241 Forte de France Cedex, Martinique, F.W.I. Tel: (596)63 00 08 Telex: CHAMCO 912 633 MR Telecopie:Fax (596)63 66 42.

Short Course: Chromatographic Separation of Enantiomers. Henry VIII Hotel and Conference Center, St. Louis, Missouri, April 24-26, 1989. Contact: Dr. Daniel W. Armstrong or Dr. Michael Van De Mark, University of Missouri-Rolla, Rolla, Missouri 65401. Phone: (314)341-4419 or 4429.

Third NAPRECA Symposium on Natural Products, ESAMI, Arusha, Tanzania, May 15-19, 1989. For details contact: Dr. M.H.H. Nkunya, Chairman Organizing Committee, Department of Chemistry, University of Dar Es Salaam, P.O. Box 35061, Dar Es Salaam, Tanzania. Tel. No. 49192 Ext. 2048, 2110, and 2113. Telex: 41327 UNISCIE TZ, 41561 UNIVIP TZ.

Sixth International Symposium on Marine Natural Products. Dakar, Senegal, July 3-8, 1989. For information contact: Pr. Jean-Michael Kornprobst, Dr. Abdoulaye Samb, Departement de Chimie, Faculte des Sciences Universite Cheikh Anta Diop de Dakar, Dakar, Senegal, Tel: 22-04-43.

V International Congress of Toxicology, Brighton, England, July 16-21, 1989. For further information contact: Secretariat, IUTOX'89 Congress House, 65 West Drive, Sutton, Surrey SM2 7NB, U.K. Tel: 01-661 0877.

The 3rd International Symposium on Poisonous Plants (formerly called the U.S./Australian Symposium on Poisonous Plants) will be held in Logan, UT, USA, July 23-29, 1989. For more information contact: Dr. Lynn F. James, USDA-ARS Poisonous Plant Research Laboratory, 1150 East 1400 North, Logan, Utah 84321, U.S.A. Telephone: (801)752-2941.

Therapy With Amino Acids and Analogues 1st International Congress, Vienna, Austria, August 7-12, 1989. For details contact: Gert Lubec, University of Vienna, Department of Pediatrics, A 1090 Vienna, Wahringer Gurtel 18, Austria, Tel. (222)4800-3232 or (evening hours): (222)23 40 424 = private. (NOTE: This meeting conflicts with our annual meeting.)

35th Congress of the International Pharmaceutical Students Federation (IPSF), hosted by the Philadelphia College of Pharmacy and Science, Philadelphia, PA, August 8-17, 1989. For further details contact: Maureen Maloney, Philadelphia College of Pharmacy and Science, Woodland Avenue at 43rd Street, Philadelphia, PA 19104. Phone: (215)596-8800. (NOTE: This meeting conflicts with our annual meeting.)

Sixth European Symposium on Organic Chemistry, September 3-8, 1989, Belgrade, Yugoslavia. For details contact: ESOC 6 Secretariat. Chairman Professor D. Vitorovic, Department of Chemistry, University of Belgrade, P.O. Box 998, 1101 Belgrade, Yugoslavia.

Nature Conservation - The Role of Corridors - Conference/Workshop, Busselton, Western Australia, September 11-15, 1989. For further information contact Miss P. Hussey, Roadside Vegetation Conservation Committee, P.O. Box 104, COMO Western Australia 6152.

SOCIETY NEWS

ASP Supports House Bill

The American Society of Pharmacognosy has voted unanimously in support of U.S. House of Representatives Bill HR 4335, The National Biological Diversity Conservation and Environment Research Act. The proposed bill sets forth a series of actions that would help prevent the loss of biological diversity through the extinction of plant and animal species. The bill would help conserve endangered species for their potential medicinal properties. The bill is expected to be reintroduced this year.

New Appointment

Philip D. Magnus, F.R.S. has recently been appointed the R.P. Doherty, Jr.-Welch Regents Chair in Chemistry at the Univ. of Texas at Austin. Congratulations!

Dedication of the Karlis K. Kazerovskis Medicinal Plant Garden

The School of Pharmacy, Ferris State University will be dedicating its Medicinal Plant Garden and Greenhouse Complex to the memory of Dr. Karlis K. Kazerovskis on April 4, 1989. His widow, Irene, will be present for the luncheon and ceremony scheduled that day, and will unveil a plaque honoring "Doc K." Dr. Kazerovskis was an honored teacher and advisor, a long-time member of the ASP and perhaps the epitome of the word "gentleman." It would be greatly appreciated if any ASP member would be willing to share their memories of Doc K. Those interested can send their thoughts to Irene, in care of Robert J. Krueger, Ph.D., School of Pharmacy, Ferris State University, Big Rapids, MI 49307, U.S.A. They will be presented to her at the dedication.

NEW MEMBERS

New Full Members

Seyed Sajadi, Seyed Aboulfazl Univ. of Shahid Beheshti, Iran

Bakolinina Andriamihaja University of Madagascar

Lakshmi S. R. Arambewela Ceylon Institute of Scientific and Industrial Research

Clarita Asibal Georgia Institute of Tech.

Stephen W. Ayer St. Louis, Missouri

M. Bapuji Regional Research Lab. Bhubaneswar, India

David T. Bailey Hauser Chemical Research Boulder, Colorado

Sudam C. Basa Regional Research Lab. Bhubaneswar, India

Salvatore Caccamese Catania, Italy

Robert W. Curley, Jr. The Ohio State University

Ermias Dagne Addis Ababa University Ethiopia

Randy Daughenbaugh Hauser Chemical Research Boulder, Colorado

John Gnabre Univ. of Arizona at Tucson

Patrick M. Gordon Organix, Inc., Woburn, MA

Tingmo Hu Dalhouse University, Canada

Hunter Jackson Natural Product Sciences Salt Lake City, UT Lydia T. Jonathan Univ. of Illinois at Chicago

Nabil Hussein El-Said Khamis National Research Center Cairo, Egypt

Randy J. Koslo Bristol-Myers Products

Gwendolyn Kydd Sterling Drug/Eastman Pharm., Malvern, PA

Terry Lemerond Green Bay, WI

Sally Look Bionetics Research, Inc. Derwood, MD

David G. Martin The Upjohn Company Kalamazoo, MI

Jim McAlpine Abbott Laboratories Abbott Park, Illinois

John C. MacAulay Red Deer, Alta., Canada

R. Kevin Pegg KM Laboratories Hillsborough, NC

Rogelio Pereda-Miranda Mexico City, Mexico

Peter K. Poole U.S. Dept. of Justice Chicago, IL

Gamini Samaranayake Virginia Polytechnic and State University

Daniel R. Schroeder Bristol-Myers Co. Wallingford, CT

Richard M. Schubert Sterling Drug, PA

Yee Seung-Jo Seoul, Korea Ellen Simpson Merck, Sharpe and Dohme, West Point, PA

Ed Smith Herb Pharm, Williams, OR

Janice Thompson Del Mar, CA

Nicholas C. Wheeler Weyerhaeuser Co. Forestry Research, Centralia, WA

Terry Marcus Wheeler Louisville, KY

Werner Wilber Foundacion La Salle De Ciencias Naturales Caracas, Venezuela

Ichiro Yasuda Tokyo Metropolitan Research Laboratories

New Associate Members

Edward K. Alstat Eclectic Institute, Inc. Portland, OR

Richard G. Bear Georgia Institute of Tech.

Ezra Bejar University of the Pacific

Yun Hua University of Maine

Charles P. Rock Gainesville, FL

Maria A. Rodriguez University of Puerto Rico Caguas, PR

Stephen B. Smith New York, NY

Carin Thomas University of Nevada, Reno

THE EDITOR'S DESK

I must apologize for the long delay since the last issue of the ASP Newsletter was published. The delay was due to the long-awaited arrival of twin boys last July which has been a real pleasure, yet very time consuming. Now that they are 7 months old, things are a little easier, and I am able to return to a somewhat normal lifestyle. I fully expect the Newsletter to return to its previous publication schedule from now on. Thank you for your patience.

I appreciate the numerous contributions which have come in for the Newsletter over the past several months. As always, I welcome any information which would be of interest to our members, including letters to the editor, publications, grant information, position openings, promotions, meeting information, books of interest, and so on. For inclusion in the Spring issue of the Newsletter, please have you contribution forwarded to me by May 1, 1989 at the following address: Joy B. Reighard, Ph.D. Editor ASP Newsletter Temple University School of

Pharmacy 3307 N. Broad St. Philadelphia, PA 19040 U.S.A.

Phone: (215)221-4946

PUBLICATIONS OF INTEREST

Washington Insight (WI), is a quarterly newsletter designed to keep natural product scientists abreast of funding opportunities and other important happenings in Washington, D.C. which may affect them and their institution. WI provides a service by which natural products scientists can have their questions, concerns, and views taken to the appropriate persons in Washington. Answers and/or reactions are conveyed by personal letter and later shared with all readers in the newsletter.

Volume I included: important policy issues, update on promising new compounds derived from natural sources, descriptions of recent regulatory changes, pertinent Congressional hearings, biotech news, interviews with Representatives Pat Williams on funding for small institutions, Claudine Schneider and James Scheuer on biological diversity, Senator Thad Cochran on a proposed natural products center at Ole Miss, and Dr. Frank E. Young, FDA Commissioner, including his comments on herbal products.

Subscribers receive Funding Alert which provides information on funding opportunities before they are advertised.

Annual subscription is \$75.00 for institutions, \$35.00 for individuals. To subscribe write to: Georgia J. Persinos, Editor, 11000 Waycroft Way, North Bethesda, MD 20852 U.S.A. Phone: (301)881-6720.

Herb Doctors, Pioneers in Nineteenth-Century American Botanical Medicine and A History of the Eclectic Medical Institute of Cincinnati, by Wade Boyle, N.D., 1988. Published by Buckeye Naturopathic Press, East Palestine, Ohio.

Advances in Electrophoresis, Chrambach, A., M.J. Dunn, and B.J. Radola, eds., Volume 1, 441 pages. VCH, 1987. \$110.00.

The Biochemistry of Plants: A Comprehensive Treatise, V.11(Biochemistry of Metabolism, 388 pages) and V. 12 (Physiology of Metabolism, 357 pages) Academic Press, 1987. \$85.00 each.

Natural Product Medicine - A Scientific Guide to Foods - Drugs - Cosmetics, Der Marderosian, Ara, and Lawrence Liberti, George F. Stickley Co., 400 pages, \$39.00. The Flavonoids - Advances in Research since 1980, J. B. Harborne, Ed., Chapman and Hall, 1988, 288 pages, Cloth - \$247.50 or Paper - \$35.00.

Fruits of Warm Climates, Julia Morton, Creative Resource Systems, Inc., 1987, 559 pages, \$75.00.

The Alkaloids: Chemical and Biological Perspectives, V. 6, S.W. Pelletier, Ed., John Wiley and Sons, Pub., 542 pages, 1988, \$110.00.

Natural Products Isolation, Gerald H. Wagman and Raymond Cooper, eds., Elsevier Science Pub., 618 pages, 1988, \$139.00.

EMPLOYMENT OPPORTUNITY

Assistant Professor of Pharmacognosy (Natural Product Chemistry)

The School of Pharmacy of the University of Connecticut is seeking nominations and applications for a tenure-track position anticipated for September 1, 1989. Applicants should have a Ph.D. in Pharmacognosy, Organic Chemistry, Biochemistry, Microbiology, or a related field; a demonstrated commitment to undergraduate and graduate education; and an established program of research related to the chemistry, biology, or biochemistry of natural products. An undergraduate degree in Pharmacy is desirable, but not essential. Applicants should forward a curriculum vitae, including graduate transcript, list of publications, and summary of research support and interests. Three letters of recommendation should be mailed directly to: Professor J.M. Edwards. Section of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, U-92, University of Connecticut, 372 Fairfield Road, Storrs, CT 06269-2092. The University of Connecticut is an Affirmative Action/Equal Opportunity Employer. M/F.

AWARDS & GRANTS

To stimulate interest in all phases of natural product research, the American Society of Pharmacognosy is offering the following awards and grants:

1. Research Starter Grants:

Members of the Society who are within the first five years of assuming their first professional position are eligible for a grant of \$2000 to \$5000 to aid in their research. These grants will not provide overhead monies to the grantee institution. Applications are due February 1, 1989.

2. Travel Grants for Active Members:

Members of the Society who are within the first five years of assuming their first professional position are eligible for a grant of \$300 to \$500 to enable them to present a paper at the annual meeting of the Society. Applications are due May 1, 1989.

3. Travel Grants for Graduate Students:

Graduate students under supervision of s Society member are eligible for a grant of \$300 to \$500 to enable them to present a paper at the annual meeting of the Society. Applications are due May 1, 1989.

4. Undergraduate Research Awards:

Undergraduate students interested in investigating a career in natural product research are eligible for a research award to study under the direction of a Society Member on the faculty of an American college or university. These awards (\$200° to the student and \$500 to the advisor) do not provide overhead monies to the grantee institution. The research project is to be accomplished in a summer during the student's academic program leading to the B.S. or Pharm.D. degrees. Applications are due February 1, 1989.

Address inquiries and requests for application information to:

Chris M. Ireland, Ph.D.
Chairman, Awards Committee
American Society of Pharmacognosy
College of Pharmacy
University of Utah
Salt Lake City, UT 84112

Dr. James E. Robbers School of Pharmacy & Pharm Sci Purdue University West Lafayette, IN 47907





ASP Newsletter Joy B. Reighard, Ph.D., Editor Temple University School of Pharmacy 3307 N. Broad St. Philadelphia, PA 19140

MEMBERSHIP

Membership in the American Society of Pharmacognosy is recognized in several categories:

Full Membership

Full membership is open to any scientist interested in the study of natural products. Dues are \$45.00 per year. If overseas airmail is requested, the dues are \$70.00.

Associate Membership

Associate membership is open to students of pharmacognosy and allied fields. These members are not accorded voting privileges, and dues are \$35.00 per year.

Honorary Membership

Honorary members are selected by the Executive Committee of the American Society of Pharmacognosy on the basis of meritorious service to pharmacognosy.

Present Honorary Members are:

Dr. Jack L. Beal, Columbus, Ohio

Dr. Norman R. Farnsworth, University of Illinois

Dr. Jonathan L. Hartwell, Washington

Dr. R. Hegnauer, Leiden, Netherlands

Dr. Albert Hofmann, Switzerland

Dr. Richard E. Schultes, Harvard Botanical Museum

Dr. Arthur E. Schwarting, Florida

Dr. Gordon Svoboda, Indianapolis, Indiana

Dr. Varro E. Tyler, Purdue University

Dr. Monroe E. Wall, Research Triangle Institute, N.C.

Dr. Heber W. Youngken, Jr., University of Rhode Island

Patron, Sustaining, and Benefactor Memberships

There memberships are open to any person or organization wishing to support the aims and objectives of the Society. Dues are as follows:

Patron Member - \$200.00 per year Sustaining Member - \$500.00 per year Benefactor Member - \$1,000.00 per year

Additional information about memberships may be obtained by writing to the Treasurer of the Society:

David J. Slatkin, Ph.D., Treasurer

The American Society of Pharmacognosy

Department of Pharmaceutical Sciences

512 Salk Hall

University of Pittsburgh

Pittsburgh, PA 15261 U.S.A.

SOCIETY BUSINESS

Nomination Committee Report

The committee has reported the following nominations for office:

For Vice President:

A. Douglas Kinghorn - The University of Illinois at Chicago Larry Robertson - The Ohio State University For Executive Committee:

Alice Clark - University of Mississippi

Robert J. Krueger - Ferris State University

The Constitution and By-Laws Committee has also proposed some minor changes which are to be voted on along with this years elections. Ballots will be sent out in the near future.