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REPORT OF A MEETING OF THE DIRECTORS OF WHO COLLABORATING CENTRES FOR ARBOVIRUSES AND HAEMORRHAGIC FEVERS

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List of Participants

Temporary Advisers

Dr J. Aaskov, WHO Collaborating Centre for Arbovirus Reference and Research Arbovirus Unit, Faculty of Science, Queensland University of Technology, 2 George Street, Brisbane, Queensland, Australia.

Dr R. d'Amelio, Italian Air Force Health Military School, V. Le P. Gobetti 2A, 00185 Rome, Italy.

Dr A. Antoniadis, WHO Collaborating Centre for Arboviruses and Haemorrhagic Fevers, Department of Microbiology, Faculty of Health Sciences, Aristotelian University of Thessaloniki, School of Medicine, 540 06 Thessaloniki, Greece.

Dr H. Artsob, Laboratory for Disease Control, Health Protection Branch, Tunney's Pasture, Ottawa, Ontario K1A 0L2, Canada.

Dr T. Avsic-Zupanc, Department of Virology, Institute of Microbiology, Medical Faculty of Ljubljana, 61150 Ljubljana, Zaloska 4, Slovenia.

Dr K. Banerjee, WHO Collaborating Centre for Arbovirus Reference and Research, National Institute of Virology, 20-A Dr Ambedkar Road, Pune 411001, India.

Dr E.K.F. Bautz, Institute of Molecular Genetics, University of Heidelberg, 6900 Heidelberg, Germany.

Dr R. Berkelman, Deputy Director, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA.

Dr A.M. Butenko, WHO Collaborating Centre for the Diagnosis of Arboviral Infections, Department of Arboviruses, Ivanovsky Institute of Virology, Academy of Medical Sciences, 16 Gamaleya Street, 123098 Moscow, Russian Federation.

Dr Chi Ming Chu, Chinese Academy of Preventive Medicine, Beijing, Peoples Republic of China.

Dr A. Chippaux, WHO Collaborating Centre for Arbovirus Reference and Research, Laboratoire des Arbovirus, Institut Pasteur, 15 rue du Docteur Roux, 75724 Paris, France.

Dr G.G. Clark, San Juan Laboratories, Dengue Branch, Division of Vector Borne Infectious Diseases, NCID, CDC, 2 Calle Casia, San Juan, Puerto Rico 00921-3200.

Dr N. Cox, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.

Dr M. Darwish, Bacteriology Department, Faculty of Medicine, Ain Shams University, Abbassia, Cairo, Egypt.

Dr J.H. Davis, Director, International Health Program Office, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.

Temporary Advisers (cont'd...)

Dr J.P. Digoutte, WHO Collaborating Centre for Arbovirus Reference and Research, Institute Pasteur de Dakar, 36 Avenue Pasteur, Dakar, Senegal.

Dr S.G. Drozdov, WHO Collaborating Centre for Arbovirus Reference and Research, Institute of Poliomyelitis and Viral Encephalitides, Academy of Medical Sciences of Russia, Moscow 142782, Russian Federation.

Dr D. Enria, WHO Collaborating Centre for Haemorrhagic Fevers, National Institute for Human Virus Diseases, Ministry of Health and Social Action, Post Office Box 195, 2700 Pergamino, Argentina.

Dr R. Graham, Naval Medical Research, Unit-2, Jakarta, Indonesia.

Dr D. Gubler, WHO Collaborating Centre for Arbovirus Reference and Research, Division of Vector-Borne Viral Diseases, Centers for Disease Control and Prevention, P.O. Box 2087, Fort Collins, CO 80522, USA.

Dr S.B. Halstead, Deputy Director, Health Sciences Division, The Rockefeller Foundation, 420 Fifth Avenue, New York, NY 10018-2702, USA.

Dr C. Hayes, Infectious Disease Program, NMRI, National Naval Medical Center, Bethesda, MD 20889-5055, USA.

Dr E. Henchal, US Army Medical Research and Development Command, Fort Detrick, Frederick, MD 21702-5011, USA.

Dr J.M. Hughes, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Clifton Road, Atlanta, GA 30333, USA.

Dr A. Igarashi, WHO Collaborating Centre for Arbovirus Research and Training, Department of Virology, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japon.

Dr P.J. Jahrling, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD 21702-5011, USA

Dr N. Karabatsos, DVBID, Centers for Disease Control and Prevention, P.O. Box 2087, Fort Collins, CO 80522, USA.

Dr O. Kew, National Center for Infectious Diseases, Centers for Diseases Control and Prevention, Atlanta, GA 30333, USA.

Dr T. Kitamura, WHO Collaborating Centre for Arbovirus Reference and Research, Department of Virology and Rickettsiology, National Institute of Health, 10-35 Kamiosaki 2-chome, Shinagawa-ku, Tokyo, Japan.

Dr T.G. Ksiazek, Special Pathogens Branch, G-14, DVRD, NCID, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329-4018, USA.

Dr M. Labuda, WHO Collaborating Centre for Arbovirus Reference and Research, Institute of Virology, Slovak Academy of Sciences, Dubravska Cesta 9, 84246 Bratislava, Slovakia.

Temporary Advisers (cont'd...)

Dr S. Kit Lam, WHO Collaborating Centre for Arbovirus Reference and Research (Dengue and Dengue Haemorrhagic Fevers), Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Kuala Lumpur 59100, Malaysia.

Dr J.R. La Montagne, Director, Microbiology and Infectious Diseases Program, NIAID, Bethesda, MD 20892, USA.

Dr B. Le Guenno, WHO Collaborating Centre for Arbovirus Reference and Research, Laboratoire des Arbovirus, Institut Pasteur, 15 rue du Docteur Roux, 75724 Paris, France.

Dr H.W. Lee, WHO Collaborating Centre for Virus Reference and Research (Haemorrhagic Fever with Renal Syndrome), Korea University Medical College, 126-1 Anam-Dong 5 GA, Seongburk-ku, Seoul 136-750, Republic of Korea.

Dr G. Lloyd, WHO Collaborating Centre for Virus Reference and Research, Division of Pathology, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom.

Dr J.S. Mackenzie, Department of Microbiology, The University of Western Australia, Queen Elizabeth II Medical Centre, Nedlands 6009, Australia.

Dr B.W.J. Mahy, Director, Division of Viral and Rickettsial Diseases, Mail Stop A-30, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.

Dr S.S. Morse, The Rockefeller University, 1230 York Avenue, Box 2, New York, NY 10021-6399, USA.

Dr L. Nicoletti, Instituto Superiore di Sanita, Laboratory of Virology, Arbovirus Unit, Via Regina Elena 299, 00161 Rome, Italy.

Dr B. Niklasson, Research Scientist, Statens Bakteriologiska Laboratorium, 105 21 Stockholm, Sweden.

Dr A.D.M.E. Osterhaus, Head, Department of Virology, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

Dr C. Oliver, Office of Health, Communicable Diseases Division, R & D/H/CD, SA-18, Suite 1200, Washington, DC 20523-1817, USA

Dr C.J. Peters, WHO Collaborating Centre for Virus Reference and Research, Special Pathogens Branch, Viral Diseases Division, Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.

Dr M. Pletschette, Science and Technology for Development Programme, Sub-Programme on Medicine, Health and Nutrition in Tropical and Sub Tropical Areas, Commission of European Community, 200 rue de la Loi, 1049 Brussels, Belgium.

Dr P. Rollin, Special Pathogens Branch, G-14, DVRD, NCID, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329-4018, USA.

Temporary Adviser's (cont'd...)

Dr S.D.K. Sempala, WHO Collaborating Centre for Arbovirus Reference and Research, Uganda Virus Research Institute, P.O. Box 49, Entebbe, Uganda.

Dr R.E. Shope, WHO Collaborating Centre for Arbovirus Reference and Research, Yale Arbovirus Research Unit, Department of Epidemiology and Public Health, School of Medicine, Yale University, 60 College Street, New Haven, CT 06510, USA.

Dr D. Snider, NCPS, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.

Dr L. Souza, WHO Virus Collaborating Centre, Virology Department, Instituto Adolfo Lutz, Ave Dr Arnaldo Lutz, Avenue Dr Arnaldo 355, GP 7027, 01246 Sao Paulo, Brazil.

Colonel E.T. Takafuji, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21702-5011, USA.

Dr R. Tesh, Yale Arbovirus Research Unit, Dept. Epidemiology and Public Health, Yale University School of Medicine, 60 College Street, P.O. Box 3333, Arbovirus Research Unit, New Haven, CT, USA.

Dr O. Tomori, WHO Collaborating Centre for Virus Reference and Research, Department of Virology, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Dr J.F. Travasso, Instituto Evandro Chagas, c/o Fundacao SESP, Caixa Postal 1530, Belem, Estado do Para, Brazil.

Dr P.M. Tukei, Virus Research Centre, Ministry of Health, Nairobi, Kenya.

Dr J. Vincent, Institut Pasteur de Bangui, P.O. Box 923, Bangui, Central African Republic.

Dr M.E. Wilson, Mount Auburn Hospital, Cambridge, MA 02238, USA.

Dr S. Yoskan, Centre for Vaccine Development, Mahidol University at Salaya, Nakhom Pathom 73170, Thailand.

WHO Secretariat

Dr K. Esteves, Technical Officer, Division of Communicable Diseases, World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland.

Dr J.W. LeDuc, Medical Officer, Division of Communicable Diseases, World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland.

Dr G. Torrigiani, Director, Division of Communicable Diseases, World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland

Dr A. Deria, Regional Advisor in Communicable Diseases, World Health Organization, Regional Office for the Eastern Mediterranean, P.O. Box 1517, Alexandria 21511, Egypt.

Dr F. Pinheiro, Epidemiology Unit, Pan American Health Organization, 525, 23rd Street, NW, Washington, D.C. 20037, USA.

1. INTRODUCTION

The WHO Collaborating Centres for Arboviruses and Haemorrhagic Fevers represents a unique, global resource composed of internationally recognized centres of excellence. While these laboratories direct their specific activities on viral diseases, they are often associated with national reference centres and Ministries of Health, so that they and their host institutions may be at the fore of current local and regional public health issues in many fields. These combined resources could contribute to the solution of global problems, not only of viral diseases, but also a number of other non-viral illnesses. It is with this potential in mind that we have organized a meeting of the Directors, not only to discuss arboviruses and haemorrhagic fevers, but also to explore the possible contribution of this network to the solution of the larger problem of emerging diseases, many of which are viral in nature. The past decade has witnessed diminished activity on the part of WHO to make maximum use of this network of Collaborating Centres, and clearly their full potential value as a dynamic, interactive network has not been attained. We hope that through this initial meeting, we can stimulate increased communications and collaborations, exchanges of information and technical resources, and enlist the Director's support in systematically addressing emerging diseases on a global scale.

Considerable attention has recently been focused on the problem of emerging infectious diseases. This interest was generated by the current pandemic of HIV and AIDS, but has its origin in the fundamental observations that microorganisms continually mutate, that human demographics and social standards change, and that the global environment is being modified. Ever-increasing movement of live animals and animal products, and changing land use are altering and expanding the geographic distribution of animal diseases, including zoonoses. Antibiotic resistance in bacteria continues to develop, leading to reduced effectiveness, increased health care costs, and needless human suffering and death when ineffective drugs are prescribed. These conditions necessitate that a coordinated, global approach be developed to systematically address emerging diseases.

2. BACKGROUND

During the past decade, numerous emerging and re-emerging infectious diseases have been recognized. In addition to HIV and AIDS, dengue haemorrhagic fever dramatically invaded the Americas, causing a massive outbreak in Cuba in 1981. More recently, dengue haemorrhagic fever has been documented in Brazil and Venezuela, and threatens other Latin American nations, as well as Asian and Pacific countries, including Australia, where dengue transmission was recently recorded in northeastern parts of the country for the first time in decades. Pandemic cholera reappeared in South America in 1991 after that region was cholera-free for many years, and a new cholera strain, V. cholerae 0139, which appears to avoid the protective immunity of persons previously infected with other strains of cholera, emerged in the Indian subcontinent. In Russia, diphtheria has made a dramatic resurgence in 1991 to 1993, and in Africa, epidemic yellow fever was recognized for the first time in Kenya. Rift Valley fever virus, an important pathogen of both domestic animals and humans, was documented in Egypt the first time since the devastating outbreak of 1977-1978, when

thousands of animals and humans were infected. Elsewhere in Africa, Lassa fever continues to cause epidemics, including nosocomial outbreaks with fatalities in doctors and nurses; and in the United States, a highly fatal form of hantavirus infection, a rodent-borne zoonosis, was recognized for the first time ever. This disease, with a clinical presentation of acute pulmonary syndrome leading to death in from 50 to 75% of those affected, is perhaps the best example of both a dramatic new disease, and of how well prepared laboratory and epidemiological investigations can be quickly mobilized to define and combat an emerging infectious disease problem.

3. OBJECTIVES OF MEETING

The meeting of Directors of WHO Collaborating Centres for Arboviruses and Haemorrhagic Fevers was convened to re-establish communications within this network of laboratories, and to enlist the support of the Directors to collaborate in a global response to emerging diseases. This network offers a unique, global resource that could play a critical role in these efforts, but due to changing priorities, reduced funding and personnel shortages, the Directors of these Centres have not met in more than a decade. Clearly the gathering was justified for purposes of rejuvenation, updating and coordinating activities alone; however, the need to enlist the support and participation of this group in a global programme to address emerging diseases added further impetus and a focal point for discussion.

The following objectives were formulated for this meeting:

3.1 To offer directors of WHO Collaborating Centres for Arboviruses and Haemorrhagic Fevers an opportunity to meet and exchange information regarding recent activities, programmes and capabilities.

3.2 To present results of a questionnaire distributed to Centre Directors regarding technical capabilities, so that common technologies, resources and short comings may be identified. This information will be used to coordinate future network activities and facilitate technical cooperation and mutual assistance among the Centres as appropriate.

3.3 To introduce and discuss the problem of emerging diseases.

3.4 To elicit the support of Centre Directors in establishing a coordinated effort to address emerging and re-emerging diseases.

3.5 To disseminate information to the Centre Directors regarding existing initiatives on emerging diseases, and other relevant surveillance activities of potential interest to the group.

4. SUMMARY OF PRESENTATIONS

A total of 11 formal presentations was made on various topics of general interest to the group. In addition, five panel discussions were held during which Directors of WHO Collaborating Centres of different geographic areas (Americas, Africa, Asia and Australia, and Europe) briefly summarized recent activity and discussed common issues. A final panel group was composed of leaders from governments and private

organizations and representatives of the WHO Regional Offices, to discuss global surveillance for new, emerging and re-emerging diseases.

Following welcoming remarks by Dr James Hughes, Director, the National Center for Infectious Diseases, CDC, Dr Ruth Berkelman discussed emerging infections and the role of global surveillance in their recognition. Her presentation clearly delineated a potential, critical role for the WHO Directors of Collaborating Centres for Arboviruses and Haemorrhagic Fevers in addressing this issue.

Results of a questionnaire sent to all WHO Collaborating Centres, and those likely to become Centres in the near future, were then presented. Thirty-five Centres were asked about their technical capabilities and routine activities in virology. To briefly summarize the findings, about three-quarters of the laboratories were directly associated with national Ministries of Health, nearly 60% were closely linked to a hospital, all trained students, and 74% currently participated in some sort of surveillance system. The most commonly used laboratory procedures were enzyme immunoassays (100%), immunofluorescent antibody assays (100%), plaque reduction neutralization tests (94%), and haemagglutination inhibition tests (91%). A number of other routine serological tests were available in many laboratories as well. Most laboratories had some molecular capabilities, including polymerase chain reaction (91%) and western blot (91%), and more than half could clone and sequence nucleic acid from specimens. Significant limitations were identified, however, in the availability of diagnostic reagents. Among the alphaviruses, only half the laboratories had reagents to diagnose chikungunya virus, and 35% had reagents for eastern, western or Venezuelan equine encephalitis viruses. For the flaviviruses, only 56% could diagnoses yellow fever, and 62% had reagents to diagnose all four serotypes of dengue. Tick-borne encephalitis could be diagnosed by 74% of the labs, but West Nile, St Louis encephalitis and Japanese encephalitis viruses could be diagnosed by half the laboratories or fewer. Pathogenic bunyaviruses could be diagnosed by few laboratories, with reagents available in 47% of the laboratories for Crimean-Congo haemorrhagic fever, 44% for at least one serotype of hantavirus, 41% for Rift Valley fever, 35% for sandfly fever, 18% for California group viruses, and 9% for Oropouche virus. Diagnosis of viruses specifically associated with haemorrhagic fever, the arenaviruses and the filoviruses, was equally limited, with only about 20-30% of the laboratories able to provide confirmation of these diseases. Among other viral diseases, 62% were prepared to diagnose HIV, 44% for rabies, 56% for polio, 59% for flu, 56% for measles, 62% for hepatitis, and 44% for rotaviruses.

The pattern that appeared from this survey was one of a network of laboratories generally well equipped and prepared to diagnose common viral diseases prevalent in their own geographic location, but often ill-prepared to diagnose viral diseases common in other parts of the world. Thus, sick returning travellers may not have their illness properly diagnosed, even if they were infected with a pathogen that was relatively common in the area visited. Hence, before this network of laboratories could be relied upon to recognized "new" or "emerging" disease, we first need to assist them to extend their capacity to diagnose "common" illnesses. Since enzyme immunoassays represent a technical capability common to all the laboratories, it follows that we should direct our efforts of capacity building at providing reagents for use in this test.

Subsequent presentations were directed toward specific technical issues and included: a summary of surveillance and control of Argentine haemorrhagic fever, including a discussion of the safety and efficacy testing of the recently developed live, attenuated vaccine for this disease; an update of the new hantavirus discovered in the southwestern United States, and the disease it causes, Hantavirus Pulmonary Syndrome; and a summary of the recent outbreak of yellow fever seen in western Kenya. The global spread of dengue and dengue haemorrhagic fever was also discussed, as were existing surveillance capabilities in Russia and the newly-independent states. Surveillance experts from the Centers for Disease Control provided overviews of two highly successful programmes, global surveillance of polio viruses, and the global network of influenza surveillance, which might serve as models for future efforts in monitoring emerging diseases. The comment was made when referring to participants in the polio surveillance efforts, that they were a "group of friends confronting a common problem". This seemed a worthy goal to create for our efforts in addressing emerging diseases.

Finally, representatives of both the US Army and the US Navy summarized their networks of overseas laboratories, including a discussion of existing capabilities in virology. It was clear from these presentations that US military research laboratories are critically important in the overall surveillance programme. Overseas laboratories and surveillance efforts of military persons deployed to high risk areas of disease can provide important information helpful to global surveillance. Reference laboratories, such as the United States Army Medical Research Institute of Infectious Diseases, where special high containment capabilities exist, provide invaluable reagents to laboratories around the world and assist in other diagnostic efforts. Infectious disease programmes at such research institutes should be well funded and integrated into the overall surveillance efforts.

Panel discussions composed of groups of the Directors of Centres in the Americas, Africa, Asia and Australia, and Europe were also held. Each Director provided brief comments regarding their respective laboratory capabilities, issues, and topics of greatest interest. Each of these presentations served to demonstrate the diversity of public health issues faced by these laboratories, and often the magnitude of specific problems. For example, the Centre in the United Kingdom, which serves as a national reference laboratory for travel medicine referrals, reported that it diagnosed approximately 1000 imported cases of dengue each year. Almost all laboratories reported dramatic increases in dengue prevalence in their areas, coupled with increasing populations of the primary vector mosquito, *Aedes aegypti.* This was especially apparent in India, where both dengue, and the more severe complications, dengue haemorrhagic fever and dengue shock syndrome, are increasingly seen. (This was followed by private discussion between Dr K. Banerjee, Dr S. Halstead, and others, resulting in a decision to organize a special meeting in Pune, India, 7-8 February, 1994, to define the problem of dengue in India, and to prepare a strategy to combat it.)

Perhaps the most troubling presentations dealt with the growing concern among Directors that the risk of urban transmission of yellow fever was increasing, and many laboratories were not prepared to diagnose this disease. This was especially apparent in Africa, but also a growing concern in the Americas. Other diseases of concern included Rift Valley fever, once again active in Egypt, and increasingly recognized in many African countries, and Japanese encephalitis, of growing importance in many parts of Asia.

The concluding discussions focused on how to organize and coordinate a global programme for emerging diseases. Key elements of such a system included having adequate technical capabilities to differentiate common from uncommon, thus being able to know when a "new" or "emerging" disease was encountered. Another critical component was improved, frequent communications, coupled with a central focal point that could distribute information and coordinate activities and responses. Finally, there was general agreement that WHO should take a leadership role in attempting to respond to this challenge, and the Directors of WHO Collaborating Centres were supportive of their active involvement in the effort.

5. RECOMMENDATIONS

5.1 WHO should take a leadership role in emerging diseases, and the WHO Collaborating Centres for Arboviruses and Haemorrhagic Fevers should play a significant part in implementation of the programme.

5.2 To maximize the contributions of the WHO Collaborating Centres in recognition and response to emerging diseases, several specific actions should be initiated:

a. Increase communications between Collaborating Centres and with WHO. This could be more frequent letters, telephone calls, facsimile messages, or greater use of e-mail, as well as more frequent meetings.

b. Provide diagnostic reagents to WHO Collaborating Centres, with the goal of being certain that each WHO Collaborating Centre has the technical capability of diagnosing common viral diseases, not only within their own area, but also among travellers or others possibly infected elsewhere.

c. To facilitate provision of these diagnostic reagents, make maximum use should be made of the existing resources already available at certain WHO Collaborating Centres, so that those Centres with expertise in a given disease can share their knowledge and reagents with others. Limited funding from WHO should be made available to facilitate production and distribution of these reagents.

5.3 Yellow fever was clearly recognized as a potentially devastating threat to much of Africa and the Americas, and special action is needed to prepare WHO Collaborating Centres to rapidly diagnose this disease, should outbreaks occur. To accomplish this, WHO should facilitate preparation and distribution of diagnostic reagents and other support material as soon as possible.

5.4 Dengue and dengue haemorrhagic fever/dengue shock syndrome are increasingly seen in tropical and subtropical countries of the world. WHO Collaborating Centres should initiate reporting of cases, especially of dengue haemorrhagic fever/dengue shock syndrome, so that the magnitude of the problem becomes more apparent. Formal or informal reporting should include copies to WHO Regional Offices, WHO Representatives at country level and WHO Headquarters to ensure maximum dissemination of information.

5.5 As outbreaks are recognized by WHO Collaborating Centres, Directors are urged to notify WHO as soon as possible, especially if technical assistance is required, and to provide brief summaries, following appropriate government clearance, to WHO Headquarters for rapid publication in the Weekly Epidemiological Record, whenever possible.

5.6 Directors of WHO Collaborating Centres were urged to obtain positive control sera, especially sera with high IgM titres, to be shared with other Centres for use in diagnostic tests. WHO should provide financial support to offset costs of the WHO Collaborating Centres in collecting and processing these sera.

5.7 The value of periodic meetings of the Directors of the WHO Collaborating Centres was stressed, and every effort should be made to schedule future meetings, perhaps in conjunction with technical conferences. The goal of meeting every two to three years was proposed.

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