The 2nd Advances Against Aspergillosis international meeting was held at the Hilton Athens in Athens, Greece, February 22-25, 2006. For this year’s meeting there were 442 registrants from 44 countries in attendance, a substantial increase from the inaugural meeting held in 2004.

The scientific program proved busy and comprehensive with 10 plenary sessions and 4 satellite symposia totalling more than 60 different speakers. In addition, two poster sessions were held to accommodate presentation of the 157 posters accepted for presentation. Abstracts on CD were distributed free to all registrants. The hoped for growth over the inaugural AAA 2004 meeting was the presentation of even greater scientific content, as indicated by the larger number of posters and more registrants and more detailed discussions and this goal clearly was attained. Moreover, several debates tackling the difficult issues of diagnosis and empiric antifungal therapy, occurred during the meeting.

Two awards for excellence were presented by David A. Stevens. The Young Investigator award was presented to S. Turnbull for her presentation of poster P015 “Transcript profiling of the murine immune response to Aspergillus fumigatus.” Authors: Turnbull S., Armstrong-James D., Bignell E., Rogers N., Rogers T., Haynes K. Molecular Mycology, Imperial College, Hammersmith Hospital, London, UK. The best overall abstract award was chosen for presentation in an oral session along with four other submitted abstracts. The talk was given by K. Buckland and the abstract is entitled “Intrapulmonary TREM-1 expression confers significant protection against chronic fungal asthma in mice by promoting clearance of A. fumiga-
In addition, 34 travel scholarships were awarded to deserving individuals to enable them to attend and further enhance their careers. These scholarships were possible because of the generous donations made to the meeting by industry and private foundations and individuals, including Schering-Plough Research Institute, ISHAM, Mira Vista Diagnostics, Foundation for Research in Infectious Diseases, David A. and Julie A. Stevens, and Advances Against Aspergillosis. In addition, the meeting organizers and scientific committee are grateful to the 13 sponsors and their generous support (For a list of the sponsors and the program of the meeting go to http://www.aaa2006.org/2006/index.php).

The social events of the meeting began with a Welcome Reception on Wednesday evening to encourage the congeniality of meeting old friends once again and meeting new colleagues. On Friday evening the conference dinner was held at the “The Old Stables”, where attendees were provided plenty of excellent Greek cuisine and drink, as well as displays of folkloric dance and music. All of the attendees appeared to enjoy the evening immensely.

A preliminary planning meeting was held to discuss possible venues and program material for AAA 2008. To date the AAA 2008 meeting will be held in the United States, likely Jan/Feb 2008, dates and location to be announced in summer 2006. In AAA 2008 the program will work to present complete issues and topics in “bench to bedside” in single sessions. The meeting Chairs and scientific committee truly wish to fulfill the needs of the Aspergillus community and as such, the continued success of this conference relies on the community’s support. We seek the continued support and welcome comments on the content, suggestions for 2008 topics, and ways to improve the meeting.

Comments and suggestions can be emailed to Drs.: Stevens (stevens@stanford.edu), Denning (ddenning@man.ac.uk), Steinbach (stein022@mc.duke.edu) or Clemons (clemons@cimr.org). We look forward to an even better conference in 2008.
Drug interactions in IA

The need to be alert to the possibility of serious drug interactions when treating patients with IA was emphasized by Russell Lewis (University of Houston, USA). The magnitude and clinical impact of these interactions were not always predictable, and lead to a need for individualized case management.

Dr. Lewis commented that all azoles had potential for drug interactions. But there were clinically important differences between the drugs. While most azoles were metabolized through phase 1 (CYP-mediated oxidative) metabolism, posaconazole was metabolized primarily through phase 2 mechanisms.

Posaconazole, like other azoles, is a potent inhibitor of CY P3A 4 but not a major substrate, so the interaction profile was different from the other azoles. “You have to know the interaction profiles of each drug. You cannot make generalizations that all azoles will interact with a particular drug,” stated Dr. Lewis.

Drug interactions that were always significant were those that affected agents with a narrow therapeutic index (e.g., immunosuppressants such as tacrolimus, chemotherapy such as vinca alkaloids) and those that increased the metabolism of antifungals (potentially resulting in ineffective treatment, such as rifamycins and phenytoin).

Also important were interactions leading to prolongation of the QTc interval. There was no doubt that antifungals, especially older azoles, could inhibit potassium channels in the heart which could lead to significant QTc prolongation and rare events of torsade des pointes arrhythmia. Ketoconazole and itraconazole had a significant risk: not only did they inhibit the metabolism of some drugs that carried high risk for torsade des pointes, they also had inherent inhibitory activity on heart tissue themselves. Many patients were taking several drugs that could prolong the QTc interval and it could be that adding an antifungal “pushes them over the edge” to arrhythmia, Dr. Lewis said.

Clinical trial methodology

In a session on clinical trial methodology, Patricia Ribaud (Hôpital Saint-Louis, Paris, France) discussed the challenges of patient recruitment for IA trials. “The main challenge is inclusion of the maximum number of patients for the minimum length of time,” she said.

One problem was that IA was not a frequently diagnosed disease: the TRANSNET surveillance programme of infection in transplant patients showed approximately a 2% incidence of IA. A iso, most recent trials tended to be non-inferiority trials and these needed many more patients than superiority trials. Recruitment would be improved by better diagnostic tools (at present, probably over 50% of cases were undiagnosed before death). A iso worth considering were “creative” trial endpoints, such as time to response or time to progression, and use of surrogate markers, such as changes in galactomannan index. This might allow shorter studies and fewer patients, Dr. Ribaud said.

Georg Maschmeyer (Humboldt University, Potsdam, Germany) spoke about the problems of defining clinical failure for salvage studies. His hypothesis was that many patients who entered a salvage trial were not really clinical failures but might be “pseudo-failures.” In some cases, benefit would then be falsely attributed to a second drug when the patient would have improved if the first drug had continued. Prof. Maschmeyer also noted that salvage therapy might in fact be combination therapy: for example, patients switched to salvage antifungal after primary therapy with high-dose liposomal amphotericin B would be getting combination therapy because of the persistence of high drug tissue concentrations.

He suggested that future salvage studies might ideally have three arms: continued primary antifungal (unless clearly inappropriate, e.g., resistance) vs. primary antifungal plus salvage antifungal vs. salvage antifungal alone.

Prof. Maschmeyer thought there was need “to cool down a bit” and not keep switching antifungals. He commented: “We have to distinguish between our nervousness and the reality.” It had not really been shown that a switch of drug was of benefit to a patient with IA who had failed full-dose modern antifungal treatment.
Pre-emptive antifungal therapy

Monica Slavin (Royal Melbourne Hospital, Australia) discussed a new approach to antifungal therapy in high-risk patients, using “pre-emptive” therapy guided by new diagnostic tests. In addition to prophylaxis for high-risk patients, the standard approach was empiric antifungal therapy, prompted by fever that was not responsive to broad-spectrum antibiotics in a neutropenic patient. “We are comfortable with this approach but there are some problems,” Dr. Slavin said. For example, empiric therapy involved treating many patients who were not going to develop infection. “Are we over-treating 90% of patients to treat the 10% who have an invasive fungal infection?” Conversely, an increasing proportion of invasive fungal infections (IFIs) occurred in the absence of febrile neutropenia (e.g., in patients with graft versus host disease) thus patients could miss out on therapy. That said, Dr. Slavin concluded, there was no doubt that outcome was better if treatment was started before infection was well established. “The ideal is to target early treatment to patients who absolutely need it. To do this, we need better understanding of how to interpret results of the non-culture diagnostic tests and work out which one, or which combinations, will be best for surveillance of patients,” Dr. Slavin said.

These non-invasive rapid IA diagnostic tests include detection of Aspergillus antigens, such as galactomannan and beta-D-glucan, and PCR-based assays to detect Aspergillus DNA. There are still a number of problems with the tests but speakers at the conference were largely optimistic that they would be useful.

Dr. Slavin said that a study had just started in Australia — the AS-PID study — looking at the impact of using PCR and galactomannan to guide antifungal therapy in patients undergoing allogeneic stem cell transplant or chemotherapy for acute leukemia. The control group was receiving the standard fever-driven approach to starting treatment. “The aim is to see if we can reduce our use of empiric antifungal therapy,” she explained.

Allergic aspergillosis

A spergillus is classified into three groups: invasive aspergillosis, chronic aspergillosis, and allergic aspergillosis. One of the major allergic diseases is allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity disease of the lungs. The evidence base for treatment of ABPA was discussed by Richard Moss (Stanford University, Palo Alto, USA). He emphasized the paucity of trial data, which was related in part to the fact that patients tended to be treated as outpatients which made trials more difficult.

Oral steroids remained the mainstay of treatment but astonishingly had never been evaluated in a randomized controlled trial, and had high toxicity. An important recent advance had been the use of itraconazole as an adjunct to steroids. There was trial evidence indicating that the antifungal had steroid-sparing effects and may have independent anti-inflammatory activity in this disease. “Evidence on itraconazole, while not overwhelming, is compelling enough to consider it as standard therapy in both asthma and cystic fibrosis patients with A BPA,” said Dr. Moss, who pointed out that risk of A BPA was now known to be higher in cystic fibrosis than in asthma.

There were limited data on other treatments, and no large controlled trials. Possibilities included inhaled steroids as alternative to systemic steroids – there was “a crying need” to find out if this was effective, Dr. Moss said. New azoles, IV pulse steroids, and nebulized amphotericin B were also possibilities.

Joanna Lumb

Pathogenesis

One of the oral sessions was dedicated to pathogenesis of aspergillosis, and a number of poster presentations dealt with aspects of pathogenesis. One of the interesting facets of the meeting was the high level of interest in secondary metabolites of Aspergillus species and the roles that these interesting compounds might play in pathogenesis, as well as how they might be exploited for identification. Nancy Keller (University of Wisconsin, Madison, USA) presented her work on the transcriptional regulator LaeA and its role in regulating expression of secondary metabolites in the gliotoxin pathway in A. fumigatus. Deletion of laeA influences the expression of pksP and rodA, as well as virtually eliminating gliotoxin production. The resulting mutants have decreased virulence in a mouse model. However, deletion of gliz, a Zn-finger transcriptional regulator specific for the gliotoxin pathway does not lead to decreased virulence in the mutant. In addition, two posters presented data examining the role of gliotoxin in patho-
genesis using mutants deleted for the gene gliP, the non-ribosomal peptidase that catalyzes the first step in gliotoxin synthesis. In the genetic background of strain A.f293, Robb Cramer (Duke University Medical Center, Durham, USA) did not find in alteration in virulence, whereas June Kwon-Chung (National Institutes of Health, Bethesda, USA), working the B-5233 background, did see a reduction. Clearly, more work needs to be done to understand the biological effects of the end products, as well as some of the intermediaries, of these highly conserved metabolic pathways.

Studying the host side of the pathogenesis equation, Scott Filler (Harbor-UCLA Medical Center, Torrance, USA) presented his in vitro model for angio-invasion in aspergillosis. By examining cytokine profile from endothelial cells grown in transwells, Dr. Filler’s group showed that endothelial cells sense whether the hyphae are penetrating them from the luminal side or the abluminal side, and respond differently to the interaction. Penetration from the luminal side actually causes more damage to the endothelial cells.

The interaction of the alveolar macrophage with the conidia of A. fumigatus was the focus of Oumaïma Ibrahim-Granet’s presentation (Institute Pasteur, Paris, France). She has previously shown that alveolar macrophages efficiently ingest and kill the conidia, and here she expanded that observation to show that activation of the ERK MAP kinase pathway is essential for this response. Treatment of the macrophages with corticosteroids blocked the ERK activation, presumably one of the mechanisms by which corticosteroid treatment predisposes patients to invasive aspergillosis. These presentations are only some of the highlights of the development of a reliable diagnostic test has proved elusive.

Dimitrios Kontoyiannis (University of Texas, Houston, USA) gave a useful review lecture which set out the current challenges associated with diagnosis. Late diagnosis is often the case and this almost certainly contributes to delay in giving effective antifungal therapy and leads to poorer outcomes for patients. He believes that over a third of cases of IA are still first diagnosed at postmortem. He pointed to the progress that has been made with publication of the widely accepted EORTC/MSG diagnostic criteria (which are in the process of being updated) although these really only apply to the setting of haematological malignancy treatment and are intended for use in research protocols.

Histological diagnosis is the gold standard but this is usually cannot be achieved. High resolution CT scans have probably made the greatest impact in recently improved clinical diagnosis, and even though characteristic abnormalities on a scan are not specific to aspergillosis they are nevertheless indicative of an invasive pulmonary fungal infection which in most centres is likely to be IA.

Within the diagnostic laboratory the focus has been on validation of non-culture based tests. Those commercially available are the Aspergillus Platelia test for detection of Aspergillus galactomannan (GM), and 1-3 beta-D-glucan (BDG) detection which is not specific for Aspergillus. The utility of the GM test was debated by Johan M. aertens (University Hospital Gasthuisberg, Leuven, Belgium) and Paul Verweij (Radboud University Nijmegen Medical Center, The Netherlands). Dr. M. aertens has shown in his patients that GM detection is a valuable diagnostic tool achieving high sensitivity and specificity. He pointed to the problems of including cases of possible IA in sensitivity analyses which made the test look less good in other published studies. Dr. Verweij has also published extensively on this test. He reviewed the problems that have been encountered with its use highlighting causes for false positive results and identifying the need for an agreed lower positive/negative cut off which the manufacturer is addressing.

Minoru Yoshida (Teikyo University School of Medicine, Kawasaki, Japan) presented data on the clinical evaluation of the BDG assay of which two are commercially available with slightly different...
protocols. Much of the early experience was from studies conducted in Japan but more recently there have been studies published from other countries which confirm the promising initial data. Dr. Yoshida felt that even though BDG detection is not specific to IA this is not a barrier to its inclusion in patient management protocols e.g., empirical antifungal therapy in febrile neutropenia. He also showed data on how the test can be used to monitor the efficacy of therapy.

Lewis White (University Hospital of Wales, Cardiff, UK) gave a well-structured lecture on where things stand with PCR assays for diagnosis of IA. The priorities are to determine the most appropriate 1) specimen to test, 2) extraction method, 3) assay design, with particular attention to minimising oligonucleotide cross hybridisation, 4) PCR platform and 5) reporting strategy.

It was somewhat disheartening to hear that automated extraction has not yet replaced labour-intensive manual protocols because there is no machine optimally designed for fungal DNA extraction although Dr. White is himself evaluating several commercially available systems. Real time PCR is now preferred but available platforms have differing performance which makes the choice of PCR platform crucial in developing a reliable assay. Dr. White is leading a consensus group which is working to establish an agreed protocol that addresses the above issues with the aim of getting PCR incorporated into consensus diagnosis criteria.

Emmanuel Roilides (Aristotle University of Thessaloniki, Greece) gave a talk on early diagnosis of IA in children. He advocated caution in using the above tests in young children because of the limited experience with their use and the problem of false positive and negative results with the GM assay.

Peter Donnelly (Radboud University Nijmegen Medical Centre, The Netherlands) reviewed the EORTC/MSG diagnostic criteria in the context of their intended use in clinical treatment trials in haematological malignancy patients. He highlighted recently identified problems with the probable and proven IA categories which tended to exclude cases of IA, while the possible IA category was likely to include too many cases that turned out not to be IA. Dr. Donnelly indicated that the revised guidelines would likely include more of the laboratory diagnostic markers discussed above although it will be interesting to see what tests are recommended.

The overall impression is that progress is being made with diagnostic tests. More laboratory validation is needed, based on consensus studies, to determine the optimal protocol; the treatment setting needs to be carefully identified; and these tests need to be studied on a prospective basis in research trials which adopt the internationally agreed diagnostic criteria.

Thomas Rogers
Host factors determining the host-pathogen interaction are crucial for the reaction pattern leading to the threat of nosocomial fungal infections. Potential fungal pathogens need to be recognized early by the host's innate immune system in order to successfully mount a defence reaction. The recently identified family of Toll-like receptors (TLRs) represents the major group of cellular signalling receptors for pathogens. Toll is a Drosophila protein involved in fungal defence and control of embryonic development. Human homologues to Toll exist and are termed Toll-like receptors. Although the term “molecular pattern” is currently widely used, it is not yet clear whether molecular patterns are recognized by this system or whether certain microbial molecules initiate the innate immune response. There is growing evidence that variations within the genes of the family of these innate immune receptors may account in part for the inherited differences in infectious disease susceptibility.

The current state of these analyses in response to Aspergillus was discussed at the recent 2nd Advances Against Aspergillosis and is summarized here.

In one Meet the Professor Session, Luigina Romani from the University of Perugia, Italy, highlighted recent findings on the TLRs and TLR-dependent signal transduction pathways that are selectively activated by the fungus. The early recognition system is largely brought about by TLR expressed on polymorphonuclear neutrophils (PMNs) and dendritic cells (DC). PMN recognition of Aspergillus occurs in a morphotype-dependent fashion, through the activation of different TLR signalling pathways. By affecting the balance between fungicidal oxidative and nonoxidative mechanisms, pro- and anti-inflammatory cytokine production and apoptosis versus necrosis, TLRs ultimately impact on the quality of microbicidal activity and inflammatory pathology. This translated in vivo in the occurrence of different patterns of fungal clearance and inflammatory pathology. Although TLRs signalling in response to Aspergillus may result in contrasting outputs in different types of effector cells, it is reasonable to believe that manipulation of TLRs by selective agonists might provoke divergent sequences and magnitudes of functional responses, so that diverse outcomes ultimately may transpire. Indeed, liposomal amphotericin B, in addition to its intrinsic antifungal activity, may activate antifungal resistance by activating TLR4 in PMNs. These studies provide a rationale to stimulate or inhibit specific classes of TLRs as a means of enhancing both innate and antigen-specific immunity to fungi. Indeed, IL-12 production by DC in response to Aspergillus conidia required the MyD88 pathway with the implication of distinct TLRs, whereas the production of IL-10 was largely MyD88-independent. Therefore, TLR collaborate with other innate immune receptors in the activation of DC against the fungus through MyD88-dependent and -independent pathways. Moreover, thymosin alpha 1, a naturally occurring thymic peptide, induced maturation and IL-12 production in DC pulsed with Aspergillus, an effect mediated by distinct TLRs. It is of interest that TLR gene expression on DC could be affected upon fungal exposure in a morphotype-dependent manner and that the TLR9 agonist CpG-ODN could convert an Aspergillus allergen to a potential protective antigen suggesting the potential for TLR agonists to act upon the degree of flexibility of the immune recognition pathways to Aspergillus antigens and allergens.

Oumaïna Ibrahim-Granet (Institute Pasteur, Paris, France) examined the TLRs and TLR-dependent signal transduction pathways that are selectively activated by the fungus in alveolar macrophages. The ERK MAPK pathways were promptly activated upon the exposure to conidia, in vitro as well as in vivo. Surprisingly, however, in vivo studies ruled out a plausible role for TLRs in the activation of the ERK MAPK pathway. Although the obvious conclusion was that
Unfortunately I missed the first congress on Advances Against Aspergillosis held at San Francisco on 2004 due to an overlap with the hunting season in the Swiss Alps, but I realize now that this was a big mistake. The second Advances Against Aspergillosis meeting in Athens was a highlight covering the many faces of research related to this complex field. Of course, one of the most important topics giving rise to deep discussions was centred on the completion of the *Aspergillus* genome projects, which will directly or indirectly influence our whole research activity on aspergillosis during the coming decades. Consequently, plenary session 7 dedicated to “Genomics and Post-genomics” was the most important for me and, perhaps, also for many other participants. I am looking forward to see the impact of this fantastic tool in *Aspergillus* research at the next AAA-meeting. The availability of the whole genome sequence will surely speed up identification of important diagnostic and therapeutic targets to be evaluated in a concentrated pharmacogenomic effort implementing all technologies involved in post-genomic research projects.

Of special interest for me were the oral presentations and posters dedicated to allergy and it will not be possible to summarize all I have learned in a short note. It is evident and known for many years, that allergy to fungi in general, and to *A. fumigatus* in particular, affects almost exclusively patients suffering from asthma or cystic fibrosis, and a subgroup of sensitized patients might develop allergic bronchopulmonary aspergillosis as pointed out by Alan P. Knutsen (Saint Louis University, USA). Allergic bronchopulmonary aspergillosis (ABPA) is a Th2-mediated hypersensitivity of the lung due to bronchial colonization with *A. fumigatus* resulting in intense inflammatory responses with severe consequences for affected patients. Although *Aspergillus* is associated with often lethal invasive diseases in immune compromised hosts, it is a far more common agent of allergy and asthma, as pointed out by Paul Bowyer (University of Manchester, UK), and this aspect has been neglected for a long time. The real problem about fungal allergy is that while everybody is aware of the existence of the phenomenon, epidemiological data allowing estimation of the dimension of the problems related to fungal sensitization is almost lacking. Exact determination of the incidence of fungal sensitization would require the availability of internationally recognized standardized fungal extracts which, unfortunately, are not available, to be used in extended skin-test surveys. As long as each laboratory uses its own in-house made extract or commercially available extracts that are...
subject to large batch-to-batch variation to perform in vitro and in vivo experiments, it will not be possible to compare the results obtained. I am convinced that the majority of the discrepancies reported between different studies are traceable to substantial differences on the quality of the extracts used to conduct the studies. Cloning, production and characterization of A. fumigatus allergens might strongly contribute to improving the diagnosis of sensitization as I pointed out in my own presentation. Unfortunately, most of the research projects are still conducted with uncharacterized extracts limiting their scientific value. Because a correct treatment anticipates a correct diagnosis of the disease, which in the case of fungal allergy is based on insufficiently characterized extracts, it is not astonishing that clinical trials aimed to treat A. fumigatus-related allergy by immunotherapy are inconclusive. Better results have been obtained with symptomatic treatments of A BPA (and partly allergy) with glucocorticosteroids as elegantly summarized by Richard B. Moss (Stanford University, Palo Alto, USA) during his critique of trials in A BPA and fungal allergy. However, also in this regard data available from the literature are fragmentary and partly contradictory. Although asthmatic patients suffering from A BPA can be successfully treated with glucocorticosteroids, the situation in CF patients affected by A BPA is much more confusing. Despite combined use of oral steroids and itraconazole reported in many studies, a demonstration that these interventions are effective needs further substantiation. The work to be done to understand immunologic responses to fungi in detail in both, healthy and allergic individuals is still long and challenging.

From my point of view the A A A congress in Athens has highlighted the weakness of the approaches currently used in diagnosis and treatment of fungal allergies, evidenced the need for coordinated action starting from the standardization of the reagents to be used up to the need for the definition of consensus regimes of treatment, and underlined the potential of the genome project to speed up rapid progress in the field. I can not imagine a better outcome from a congress and I am grateful to the organizers for the tremendous amount of work done to create an international discussion platform which, I am absolutely sure about this point, will not fail to strengthen existing and start new collaborations in the field of aspergillosis.

Reto Crameri

Music and dance during the conference dinner at “The Old Stables”
Our 13th anniversary

Last year a voting round among the Council membership for the new president of ECMM ended up with a close finish between several candidates. I have the honour of serving the Confederation for the next 3 years. The road has been paved and widened by my three excellent predecessors Prof. Bertrand Dupont (1993-1999), Rod Hay (1999-2002) and Frank Odds (2002-2005). I congratulate them with the 13th birthday of ECMM and thank them for the creation of our confederation as it stands now. I see it as my task for the next years to come to construct side roads and connections to other areas of infectious diseases in Europe and bring basic mycology together with clinical mycology. Our Trends in Medical Mycology Congress is the starting point of the latter goal. The last year and this year we are blessed in Europe with two high quality mycology meetings, TIMM2 and the International Society for Human and Animal Mycology Congress. Profs. Markus Ruhnke and Georg Masmey were responsible for the smooth and successful organisation of our bi-annual conference last fall in Berlin and Prof. Dupont, one of the founding fathers of ECMM, is preparing the world conference on mycology, ISHAM, coming June in Paris. And this is not all. Preparations towards TIMM3 in October 2007 in Torino, Italy have started and are on track. Our Italian colleagues Profs. Marianna Viviani and Claudio Viscoli, as national organizers, distributed the first announcement at the last European Society of Clinical Microbiology and Infectious Diseases meeting in Nice and you will hear more about Torino in the coming months. This year it is time to plan our first educational meeting for 2008 and I urge National Societies to express their interest in hosting TIMM4 in 2009, to contact the secretary of ECMM via their Council Member.

The Council meeting in Berlin appointed Dr. Maiken Cavling Arendrup, President of the Nordic Society for Medical Mycology, in the Executive Committee for organizing the next two TIMM conferences together with Prof. Thierry Calandra as representative of the EORTC-Infectious Diseases Group. Everybody recognizes the necessity of a well designed and smoothly running website to enhance

Jacques F. Meis

(continued on page 4)