Mycology newsletter

The ECMM/CEMM Mycology Newsletter is mailed to the members of the national societies affiliated to the European Confederation of Medical Mycology (about 3000 in 20 different countries)

2/99

ECMM
European Confederation of Medical Mycology
CEMM
Confédération Européenne de Mycologie Médicale

Message from the President

The start of the new millennium is an excuse for many celebrations and a time to review the events of the preceding years. In Medical Mycology it provides the opportunity to look back over the past hundred years. Since the beginning of the century there have been staggering advances in all areas of infectious disease. The early 1900's saw a rapid succession of publications recording the first clinical cases and the morphological descriptions of the fungal causes of a large number of diseases. But by the end of the century there is a closer understanding of the molecular and cellular mechanisms that underlie morphogenesis, immunity and virulence. Although there is much that remains to be done the pace of scientific discovery has been dramatic and it appears to be accelerating. These advances have also been accompanied by set backs, notably the development of resistance to antimicrobials. Initially drug resistance was thought to be largely confined to antibacterials, but it is abundantly clear that antifungals along with antivirals and other antimicrobial agents are also subject to resistance and that through adaptation and mutation organisms evade some cidal or static drug mechanisms.

The rise of antimicrobial resistance is an issue which has reached the public domain, and this, coupled with the spread of new infective processes such as HIV and a resurgence in old disease including tuberculosis and meningococcal infections, has alerted politicians and the general public to the fact that infectious diseases still pose a significant threat. Whatever the background and notwithstanding the tendency of the lay press to misinterpret the consequences of this change in the importance of infections in national health, the renewal of public and political awareness may be of indirect help to our speciality. There is likely to be a renewed focus of interest and, as a consequence, increased spending on the prevention and recognition of infectious diseases in the early part of the next century. We must ensure that Medical Mycology will benefit from this process.

Roderick J. Hay, ECMM President

At the 1999 meeting in Dresden we had a full and well-organised programme with both scientific and social highlights. The organisers are to be congratulated on this meeting, which was a memorable one. At the meeting a number of changes were approved in the organisation of the

(continued on page 3)

Contents

ECMM/CEMM

Mycology Newsletter

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Vicepresident: R.M. Velho
Secretary: M.L. Rosado *(ECMM delegate)*
Treasurer: M. Gardete
Membership 1999: 50
Newsletter

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Secretary: S. Santamaría del Campo
Treasurer: A.J. Carrillo Muñoz
President Medical Section: F.J. Cabañes Saenz *(ECMM delegate)*
Membership 1999: 92
National meeting: November 8, 2000, Barcelona (joint with ECMM Congress)
Journal: Revista Iberoamericana de Micología

British Society for Medical Mycology (BSMM)
President: R.J. Hay *(ECMM delegate)*
General Secretary: R.A. Barnes
Meetings Secretary: D. Sullivan
Treasurer: G.S. Shankland
Membership 1999: 255
National meeting: April 3-4, 2000, Stratford upon Avon
Newsletter

Bulgarian Mycological Society (BMS)
President: T. Kantardjiev *(ECMM delegate)*
Vicepresident: G. Mateev
Secretary: A. Kouzmanov
Treasurer: T. Velinov
Membership 1999: 31
National meeting: November 23-25, 2000

Czech Mycological Group
ECMM delegate: A. Tomsíková

Danish Society for Mycopathologia
President: N.A. Peterslund
Vicepresident: L. Larsen
Secretary: J. Stenderup *(ECMM delegate)*
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Membership 1999: 45

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Vicepresident: H. Hof
Secretary: C. Seebacher
Treasurer: W. Fegeler
ECMM delegate: H. Bernhardt
Membership 1999: 1100
National meeting: September 14-16, 2000, Berlin
Journal: Mycoses

Federazione Italiana di Micopatologia Umana e Animale (FIMUA)
President: E. Concia
Vicepresident: M.T. Montagna
Secretary: A. Persi
Treasurer: A.M. Tortorano
ECMM delegate: M.A. Viviani
Membership 1999: 160
National meeting: September 7-9, 2000, Bari
Newsletter

Finnish Society for Medical Mycology
President: J. Issakainen *(ECMM delegate)*
Vicepresident: A. Kahanpää
Secretary: P. Kankaanpää
Treasurer: H. Mussalo-Rauhamaa
Membership 1999: 56
National meeting: March 2000 (to be confirmed)
Newsletter

Greek Mycological Group
ECMM delegate: O. Marcelou-Kinti

Hungarian Dermatological Society - Mycology Section
President: G. Simon *(ECMM delegate)*
Secretary: G. Fekete
Membership 1999: 37
National meeting: 2000, Budapest (to be confirmed)

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President: E. Segal
Secretary: I. Berdicevsky *(ECMM delegate)*
Treasurer: D. Elad
Membership 1999: 80

Polish Dermatologic Society Mycology Section
President: E. Baran *(ECMM delegate)*
Vicepresident: P. Ratka
Secretary: J. Szepietowski
Treasurer: R. Bialynicki-Birula
Membership 1999: 98
National meeting: September 2-4, 2000, Poznan
Journal: Mikologia Lekarska (Medical Mycology)

Netherland Society for Medical Mycology (NVMy)
President: J.F.G.M. Meis *(ECMM delegate)*
Scientific Secretary: G.S. de Hoog
Secretary: E.P.F. Yzerman
Treasurer: R.W. Brimicombe
Membership 1999: 137
National meeting: April 18, 2000

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Vicepresident: V.B. Antonov
Secretary: N.M. Vasilyeva
Treasurer: I.V. Kurbatova
Membership 1999: 25

Société Belge de Mycologie Humaine et Animale/ Belgische Vereniging Voor Menselijke en Dierlijke Mycologie
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Vicepresident: N. Lateur, E. Van Hecke
Secretary: P.E. Lagneau, J. Boelaert
Treasurer: F. Symoens
ECMM Delegate: D. Swinne
Membership 1999: 180
National meeting: September 2000 (to be confirmed)

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President: Cl. de Bièvre
Vicepresident: D. Chabasse, O. Morin, H. Koenig
Secretary: B. Dupont *(ECMM delegate)*
Treasurer: P. Boiron
Membership 1999: 340
National meeting: October 9-14, 2000, Cayenne (French Guyana)
Journal: Journal de Mycologie Médicale

Swedish Society for Clinical Mycology
President: J. Faergemann
Vicepresident: T. Kaaman
Secretary: G. Pålsson
Treasurer: S. Johansson
ECMM delegate: L. Edebo
Membership 1999: 105
National meeting: April 2000, Göteborg
Newsletter

Swiss Mycological Group
ECMM delegate: M. Monod

Turkish Microbiological Society Mycology Section
President: Ö. Ang
ECMM delegate: E. Tümbay
Membership 1999: 21

(Information provided by the member Societies)

Message from the President

(continued from page 1)

ECMM with a new Treasurer, Dr Youni Issakainen - our indefatigable Secretary was persuaded to remain - and a new President. Finland was welcomed to the ECMM fold and our Hungarian colleagues have offered to host the meeting in 2002. The ECMM is now well established and its future assured. I would like to thank my predecessor, Bertrand Dupont, for all the hard work he has put in to ensure the success of the ECMM and our last Treasurer, Lars Edebo, who has managed to keep us solvent and in good financial shape for the future.

It just remains for me to wish everyone a happy New Year and a bright mycological future.

Roderick J. Hay

The Finnish Society for Medical Mycology

Dear Colleagues,

The Editor of the ECMM Newsletter and our General Secretary, Maria Anna Viviani, kindly suggested me to write a short introduction of the new Finnish Society for other ECMM members. I feel very happy and privileged to do so.

For some less travelled ECMM members, the image of Finland may still be that of an arctic tundra where fierce hunters must use most of their time for tackling wolves in their reindeer sleighs. It is not quite so.

Finland has nearly the area of Germany but in somewhat harsher climatic conditions. Our natural vegetation largely consists of coniferous forest which is dotted by thousands of shallow lakes and bogs. Our country is covered by snow - and our waters by ice - about five months per year. This environment has supported the living of only 5 million Finns, about 6% of the number of people in Germany.

Before the World War II, Finland lived mainly from agriculture and forestry. After that, through a rather isolated position during the Cold War, the picture has changed to that of an industrial country producing paper and technology to all countries, the phone company Nokia as a recent example. Now in 1999, Finland has a covering public health care system, the highest percentage of Internet connections in the world, and - by chance - the Presidency of the EU.

The opening has had also side effects: life and environment have been commercialized, services in the countryside are diminished and people are moving to hastily built suburbs. Unemployment and narcotics are growing problems among some of our young. We are still looking for a healthy identity in the global market square.

In this historical setting, the roots of our medical mycology have grown from tiny branches from various fields. Some dermatologists, such as our honorary member C.E. Sonck (born in 1905) and I. Helander, have for long treated and studied mycoses of the skin. The two largest medical mycology laboratories (in Helsinki and Turku), although now dealing with all kinds of specimens, were originally founded in university dermatology clinics in late 50'ies.

Fungi have also interested some internal medicine pioneers of the field, such as A. Kahanpää and R. Visakorpi, but only the recent boom of immunocompromised patients has really put opportunistic fungi on the stage. Several of our members such as V.-J. Anttila and J. Salonen are actively studying systemic fungal infections. Other fields of medicine, such as dentistry (M. Lenander-Lumikari) and pathology (J. Laine) add their valuable points of view in our Society.

Partly because of the rapidly built houses in our moist climate, there has been a strong research input in Finland for mouldy environments, aerobiology and occupational health. These fields are well represented in our society, only to mention A. Nevalainen, A. Rantio-Lehtimäki and H. Mussalo-Rauhamaa. In some teams, emphasis has been put on the immunology of these conditions.

Our veterinarian members have made long careers in mycology, notably E.-L. Hintikka and R. Aho with mould toxins and zoonotic fungi, respectively. Some of us have also an interest on mycotoxins of human food, such as our Secretary P. Kankaanpää and S. Salminen.

Many of us have a background in diagnostic medical microbiology, exemplified by T. Ojanen, A. Nissinen and P. Kuusela. Also many skilled laboratory nurses and technicians - whose work makes the solid foundation of all diagnostic work and research - are active members of our Society. M. Mikkola, M. Castrén, S. Kirjanen, A. Koskensalo and E. Tunnela, already, have a sum working experience of more than a hundred years.

Although there is an old, esteemed society in Finland for promoting knowledge on macrofungi, we have purposefully included also the aspects of general mycology and poisonings by macrofungi in our spectrum of interests. To mention only one natural reason, general mycology provides the medical community with basic knowledge on fungi - their classification, structure and biology. The enormous diversity of fungi makes us humble: all species and their biologies are impossible to be mastered through any single peeping hole. For instance, the first appointed Medical Mycologist in Finland, the late A. Salonen who preceded P. Koukila-Kähkölä in Helsinki, was originally a plant pathologist. We are happy to enjoy the memberships of top general mycologists such as J. Vauras, Y. Mäkinen and L. Kosonen.

Some current topics not mentioned above are molecular classification of fungi, represented by T. Yli-Mattila and J. Jalava; national quality control organized by R. Myllys; and standardization of laboratory procedures, much developed by O. Liimatainen.

When our Society was founded in 1998 by 24 members, one of our core ideas was to create bridges between people both "horizontally" - meaning between different fields of science - and "vertically" - meaning workers on different steps of education and office hierarchy. The variety of backgrounds among equal members of the Society has resulted in fruitful discussions and better understanding of this wide and fascinating field. As fora of this process we have the annual meetings, a national newsletter Sienet ja Terveys («Fungi and Health») and national courses. We have just exceeded the number of 50 members.

Based on the above short introduction, I hope that you, dear ECMM members, would not see Finland as something cold somewhere far away, but as a Nordic country where you already have a ready network of friends and colleagues. Whether you will wish to cooperate in professional affairs or visit our country privately, please feel free to contact our Society. You are always welcome.

Yours, sincerely

Jouni Issakainen
Chairman
Finnish Society for Medical Mycology

Barcelona 2000:
the 6th Congress of the ECMM

by Josep M. Torres Rodriguez
President of the Spanish Society of Mycology
President of the Organizing Committee of the 6th Congress of the ECMM

On behalf of the Organizing Committee and as the President of the Spanish Society of Micology, I have the honour of presenting the 6th Congress of the CEMM, to be held in Barcelona on 9-11 November of the year 2000.

Barcelona is an attractive city in the North-East of Spain, on the Mediterranean Sea. It has hosted many major scientific and cultural events, among which are congresses such as the International Society for Human and Animal Mycology (ISHAM), held in 1988, and of which many mycologists still have happy memories. On this occasion, we have been granted the organization of the first Congress of the 21st century of the powerful European Confederation of Medical Mycology which we also helped to found.

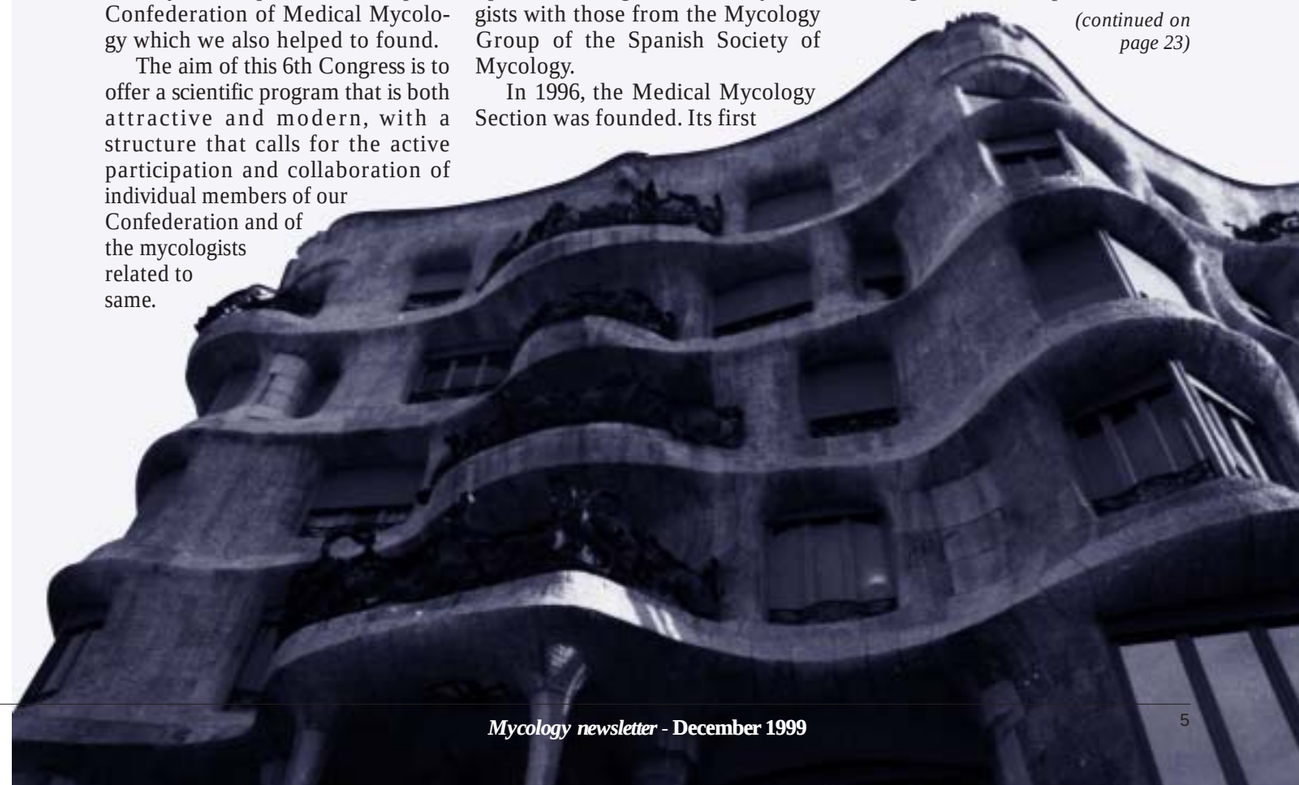
The aim of this 6th Congress is to offer a scientific program that is both attractive and modern, with a structure that calls for the active participation and collaboration of individual members of our Confederation and of the mycologists related to same.

The AEM: Asociación Española de Micología (Spanish Society of Mycology, ex-Spanish Society of Mycology Specialists), was founded in 1977 soon after the advent of democracy in Spain that enabled the foundation of societies without the restrictions marked by the old regime. Through its statutes, the AEM proposes to promote Mycology in all its aspects and foster scientific exchanges with similar Societies. It is not accidental that shortly after its foundation, its first President - Jaume Borrell - requested admission to ISHAM: moreover since 1980 Joint Mycology Meetings - at present National Mycology Congresses - have been held in Spain, reuniting the AEM mycologists with those from the Mycology Group of the Spanish Society of Mycology.

In 1996, the Medical Mycology Section was founded. Its first Coordinator was Dr. Jose Pontón, a renowned mycologist of the University of the Basque Country. Despite its recent foundation, this Section has already organized courses, meetings and round tables within National Congresses and it will be responsible for opening the European Meeting. This first autonomous Scientific Conference will be presented the day before the beginning of the 6th Congress. Its theme will be *Aspergillus and Aspergillosis*, a very topical subject since there have been several outbreaks of hospital infection recently throughout the country.

In Spain, Medical Mycology is not a very well developed specialty although renowned specialists such

(continued on page 23)



Development and registration of the reagents for the in vitro diagnosis: Which perspectives for Medical Mycology?

Dear Colleagues

In the previous issue, the Mycology Newsletter reported the results of an enquiry carried out among the affiliated Societies in order to know the situation in the different European countries concerning the regulatory status of reagents for *in vitro* diagnosis and their evaluation pre and after marketing (ECMM Mycology Newsletter 1/99, page 7).

The information received from the ECMM delegates showed that at present the registration is mandatory only in some countries, but different procedures are followed. In France, the registration of reagents for *in vitro* diagnosis requires that a dossier is submitted by the manufacturer to the Agence Française de Sécurité Sanitaire des Produits de Santé for final examination and administrative approval. Also the reagents either produced in other countries or in France have to be submitted to this procedure. This law intended to ensure the quality of the product contributing to the quality of the analysis.

In most of the European countries the lack of registration enables the distribution of reagents with no obligation of technical and administrative expertise.

The European Directive

The awareness of this problem have stimulated the European Parliament and Council to produce the Directive 98/79/EC. The objectives of this Directive are:

- to remove any barrier to free trade and ensure, under the best safety conditions, free movement of the *in vitro* diagnostic medical devices,
- to harmonize rules in the Members States of the European Union with regard to the safety, health protection, performance, characteristics and authorisation procedures for *in vitro* diagnostic medical devices.

According to the Directive (article 1, 2b), *in vitro* diagnostic medical devices mean «any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:
- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures».

The new approach defines, for the purpose of the conformity assessment procedures, two main classes of the *in vitro* diagnostic medical devices.

The class I includes most of such devices which do not imply a direct risk to patients and are used by trained professionals. These devices can be marketed after notification to the competent authorities by the manufacturer, who ensure the conformity to the essential requirements for CE marking, including Quality System, Risk Analysis and Vigilance.

For these devices, distributed without a previous control, in case a Member State ascertains that a device may compromise the health and/or safety of patients, it can withdraw such device from the market, immediately informing the Commission of such measure indicating the reason for its decision.

The class II includes specific devices the correct performance of which is essential to medical practice and the failure of which can cause serious risk to health. For these devices the intervention of notified bodies is needed. Among these devices, the products used in blood transfusion and the prevention of AIDS and certain types of hepatitis require a specific conformity assessment. After this, the notification is the same than for Class I products.

All the reagents included in Class II are listed in the Annex II of the Directive; the remaining are automatically included in Class I.

All mycological devices are in Class I, also those involved in the diagnosis of invasive mycoses, which are life-threatening diseases.

What ECMM can do

This classification makes more important the need for a standardization of the procedures in Medical Mycology which are lacking in Europe. We urgently need to reach a consensus on the standardization of the diagnostic methods and on the specifications of the diagnostic devices, so that recommendations can be given which can be used by manufacturers in the preparation of their products and by those who will evaluate and use the marketed diagnostic devices.

The ECMM has the authoritativeness and the scientific competence needed to reach this goal.

Renée Grillot

The IVD Directive has been published in the Official Journal of the European Communities on December 8, 1998. From this date, the Directive entered into force.
The text of the IVD Directive can be found, free of charge, on the Europa Web site:
http://europa.eu.int/eur-lex/en/oj/index.html

Next steps:

December 7, 1999	**End of transposition period** The transposition into national laws must be completed by the Member States.
June 7, 2000	**1st possible CE mark** Member States apply the provisions of the Directive. After June 2000 and during a transition period, CE-marked and non CE-marked devices can be placed on the market, i.e. companies may choose to follow either the European Directive (CE Mark) or the national legislation, if existing (If not, the devices can be freely placed on the market).
December 7, 2003	**End of transition period for placing on the market*** Only CE-marked devices can be placed on the market
December 7, 2005	**End of transition period for putting into service**** Only CE-marked devices can be put into service

*Placing on the market: "*The first making available in return for payment or free of charge of a device other than a device intended for performance evaluation, with a view to distribution and/or use on the Community market*".
**Putting into service: "*The stage at which a device has been made available to the final user as being ready for use on the Community market for the first time of its intended purpose*".

Why don't we try again from Europe?

In these last years much effort has been spent in producing and organizing biological data in databases now entered in the everyday life of all researchers. The enormous flow of informations and the extreme ease to obtain them can sometimes bring about the idea that data are indeed the ultimate result of the scientific research and place data and concepts on the same level. This trend has been made plain by the reduced attention on logic or, using a reductive view, on epistemology.

Still, the concept is the main instrument of knowledge so far forged by the human brain and inherently contains the achievement of a consensus among the people that have discussed on a specific concept. In this way, discussion is the essential mechanism through which different data are taken into consideration to reach an universal and consistent definition admissible and agreeable for any further use and research.

Very often, modern scientific literature shows a remarkable lack of discussion: some papers are essentially cited by further papers of the same group, some others are simply ignored, very few are subject to an objective and constructive criticism. There are surely many reasons for this phenomenon, one could be found in the peer reviewing system that confines all criticism to this part of the process to accept a paper. Unfortunately, as everybody knows, the referees criticism is very rarely open to any sort of discussion and, in any case, remains restrained between authors and referees.

A new style of research strongly calls for an open discussion fully visible on our scientific journals. We should maybe have the nerve to go back to the way of writing of a few decades ago when, for instance, Winge and Lindegren had an open and hard dispute on the homo-heterotallic nature of *Saccharomyces cerevisiae*.

Why do not we try again? Why do not we devote at least a little section of our journals to disputing papers? This invitation is addressed to all editors, but with a special emphasis to those working in Europe where concept and dispute were born and grew in the past twenty-five centuries, to help producing large and remarkable parts of our present culture.

Gianluigi Cardinali

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Chronic mucocutaneous candidosis:
an invitation to collaborate in establishing a European database

Chronic mucocutaneous candidosis (CMC) is a rare syndrome which usually presents in early childhood with persistent oropharyngeal *Candida* infections which may then extend to the skin and nails. Associated abnormalities include endocrinopathies, auto-immune diseases, such as pernicious anaemia and alopecia areata, and bronchiectasis.

At least half the patients have a family history of the disease which appears to be inherited as either a recessive or an autosomal dominant trait with or without endocrine disease such as hypothyroidism. The condition is therefore a potential model for studying the relationship between specific mutations and susceptibility to infection as well other conditions such as autoimmunity.

The best way of approaching an understanding of the genetic basis of CMC is to study a suitable cohort of families where there are both affected and unaffected individuals. The purpose of this enquiry is to set up a database on CMC in Europe in order to establish whether there are sufficient numbers of patients with CMC and associated disorders to justify a study of the genetic basis of the disease.

I would be very interested to hear from anyone who has any patient with CMC with or without a family history or who can pass on the request to a colleague. I can send them by e-mail (or fax) an appropriate short questionnaire in order to establish the numbers of patients in each clinical category who might form the basis for a pan-European study of susceptibility to chronic mucocutaneous candidosis.

At this stage we would hope to establish whether there are sufficient numbers of patients and the interest to take the project further. Any expression of interest at this stage does not commit you to further involvement!

Roderick J. Hay

My e-mail is: HYPERLINK mailto: r.hay@umds.ac.uk
or you can send a fax to: +44 171 960 5802
An alternative would be to write to me: Professor R.J. Hay
St Johns Institute of Dermatology
St Thomas Hospital
London SE1 7EH, UK

Cat and Dog: epidemiological Survey of dermatophytosis in Europe

In pets, *Microsporum canis* is the most frequent cause of dermatophytosis in Europe. Cats are accepted as the principal resevoir for this species, and transfer it to owners and to other animals in contact with them, particularly dogs.Therefore, the incidence of dermatophytosis varies according to climate and with the natural resevoirs. The pattern of the species of dermatophytes involved in dermatophytosis may be different in similar geographical conditions, both in humans and animals, and it has been related, among other factors, to the decline in the incidence of animal ringworm in these areas or the degree and closeness of animal to human contact.

The objective of this retrospective survey is to identify the main dermatophytes species involved in cat and dog ringworm over the five year period 1995-1999 in different European countries.

Investigators interested in participating to this study as “national coordinator” are requested to fill the following form. We would like hear from all interested individuals or groups, taking in consideration the need to obtain representative information from different region in Europe. Authorship of the data will be protected according to the “Rules for Epidemiological ECMM Working Group” (see Mycology Newsletter 0/97, page 5).

Name .....

Title .....

Address .....

Country .....

Phone .....

Fax .....

E-mail .....

Thank you for your interest.
Please return to

Prof. Francisco J. Cabañes Saenz
Departament de Patologia i Producció Animals
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CAT AND DOG: EPIDEMIOLOGICAL SURVEY OF DERMATOPHYTOSIS IN EUROPE (1995-1999)

CAT

TOTAL ANIMALS EXAMINED: ..... (male ..... / female .....)

Positive animals: ..... (male ..... / female .....)

AGE GROUP *specify the age group in which the occurrence of dermatophytes was the highest reported*

<1 year ..... 1-5 years ..... >5years .....

SEASONAL TREND *specify the month in which the number of positive cases was the highest reported*

month ..... animals examined ..... positive .....

BREED *specify the five breeds in which the prevalence of dermatophytoses was the highest reported*

1st ..... animals examined ..... positive .....

2nd ..... animals examined ..... positive .....

3rd ..... animals examined ..... positive .....

4th ..... animals examined ..... positive .....

5th ..... animals examined ..... positive .....

MICROSCOPIC EXAMINATION OF SPECIMENS .....

Percentage of positive microscopic examinations in culture positive submissions: .....

Technique used: ..... % KOH

..... % NaOH

..... % KOH+ lactophenol (cotton blue)

..... % KOH+ .....

..... % other *please specify* .....

Isolation agar medium used (routine) .....

DERMATOPHYTES ISOLATED *specify the number of isolates of each species; please do not include species considered as rarely pathogenic dermatophytes or their infections are cited as questionable, such as* M. cookei, T. ajelloi *or* T. terrestre

- *M. canis* .....
- *T. mentagrophytes* .....
- *M. gypseum* .....

....

....

CAT AND DOG: EPIDEMIOLOGICAL SURVEY OF DERMATOPHYTOSIS IN EUROPE (1995-1999)

DOG

TOTAL ANIMALS EXAMINED: ..... (male ..... / female .....)

Positive animals: ..... (male ..... / female .....)

AGE GROUP *specify the age group in which the occurrence of dermatophytes was the highest reported*

<1 year ..... 1-5 years ..... >5years .....

SEASONAL TREND *specify the month in which the number of positive cases was the highest reported*

month ..... animals examined ..... positive .....

BREED *specify the five breeds in which the prevalence of dermatophytoses was the highest reported*

1st ..... animals examined ..... positive .....

2nd ..... animals examined ..... positive .....

3rd ..... animals examined ..... positive .....

4th ..... animals examined ..... positive .....

5th ..... animals examined ..... positive .....

MICROSCOPIC EXAMINATION OF SPECIMENS .....

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..... % other *please specify* .....

Isolation agar medium used (routine) .....

DERMATOPHYTES ISOLATED *specify the number of isolates of each species; please do not include species considered as rarely pathogenic dermatophytes or their infections are cited as questionable, such as* M. cookei, T. ajelloi *or* T. terrestre

- *M. canis* .....
- *T. mentagrophytes* .....
- *M. gypseum* .....

....

....

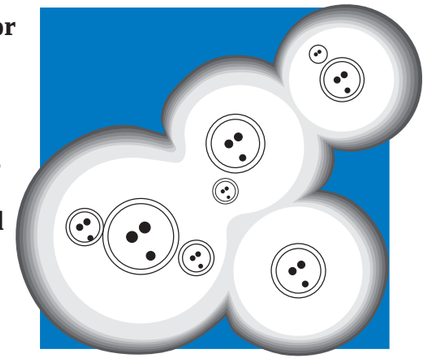
Special report on...

by
Elisabetta Blasi, Tania Pfeiffer, Tania Sorrell, and Brian Wickes

4th International Conference on Cryptococcus and Cryptococcosis

The Royal Society in London recently served as the venue for the 4th International Conference on Cryptococcus and Cryptococcosis and it was my pleasure, along with my colleagues Rod Hay and Ken Haynes, to welcome over 170 delegates from around the world. The format of the meeting was altered somewhat compared to the 3rd International Conference, with many more submitted papers given as oral presentations - this proved a successful change and the standard of papers presented was uniformly high. We were particularly pleased to see so many younger people at the meeting, and we wish to thank the Burroughs Wellcome Fund, The Welcome Trust and the British Society for Medical Mycology for allowing us to offer 22 young investigator scholarships. Unfortunately the London weather was not all that it could have been, but we hope everyone enjoyed the Conference dinner in the Natural History museum - its not everyday you have dinner with a dinosaur! I would like to say a special thank you to all our commercial sponsors, without which the conference could not have taken place, and to my staff and to the staff of Gemini International who were superb in helping to run the conference. Finally thanks to all the delegates for making the meeting such a success. The 5th International Conference will be in Adelaide and I am sure that David Ellis, Tania Sorrell and colleagues will organise a marvellous meeting.

Andy Hamilton



chaired by
Ken Haynes and Yun Chang (I)
and Brian Wickes and John Perfect (VII)

Session I & VII

Molecular biology and biochemistry

The fourth International Conference on *Cryptococcus* and Cryptococcosis opened, as usual, with a session on molecular biology and biochemistry. What was unusual at this meeting was that four days later, the meeting closed with a session on molecular biology and biochemistry. All totaled, there were 21 talks and 24 posters in this area. The two sessions on molecular biology and biochemistry (as well as an update on *Cryptococcus neoformans* genomics) were an indication of how fast the field has advanced as well as where it is headed.

The morning session of molecular biology/biochemistry (first session) was dominated by talks on mating and mating type. Brian Wickes described the first *MATa*-specific mating gene, the *MATa* pheromone. The gene, which was found to be typical of other fungal pheromone genes, functions in a manner analogous to the previously described *MATalpha* pheromone. It is multicopy and defines the *MATa* mating type locus although it appears to be specific for serotype D strains. Preliminary data suggest that the *MATa* locus will be just as large as the *MATalpha* locus. Joseph Heitman presented evidence that *C. neoformans* possesses two parallel signaling cascades which respond to either pheromone or starvation. His laboratory has identified homologs of RAS, adenylyl cyclase, and cAMP protein kinases which respond to nutritional cues. They have also isolated homologs of *STE20* and *FUS3* (*CPK1*) which respond to pheromone and confer a sterile phenotype when disrupted.

Ping Wang described a related gene, *GPB1*, which is a G-protein β subunit that is distinct from *GPA1*

Brian Wickes

and regulates haploid fruiting and mating. *GPA1* conversely, regulates mating and virulence. Andrew Alspaugh characterized among other genes, *RAS1* and *CAC1* (adenylate cyclase) and found that *cac1* mutants are similar to *gpa1* mutants while *ras1* mutants are unable to grow at elevated temperatures. *Ras1* mutants also show a reduced ability to form melanin, a known virulence factor of *C. neoformans*. In yet another related topic to mating and mating type, Yun Chang demonstrated that *ste12alpha* mutants are greatly reduced in virulence, a key association between mating type and virulence since *STE12alpha* is only found in *MATalpha* cells. He showed that these mutants are also reduced in the ability to form capsule and melanin under certain growth conditions thereby providing a molecular link between mating type and virulence.

In the second half of this first session, more varied molecular and biochemical data were presented. Raj Pandrangi has created a recombinant adenovirus shuttle vector that can be used to express a mouse granulocyte-macrophage colony stimulating factor (GM-CSF). Once transfected, this vector will be used to evaulate GM-CSF expression as a method for clearing *C. neoformans* infections from the lung.

Throughout the meeting there were a number of presentations on *C. neoformans* phospholipases. Sharon Chen presented a talk which continued her previous studies on phospholipase B. She has recently purified phospholipase B from *C. neoformans* and found that the enzyme is capable of degrading phospholipids which are found in the human lung. The enzyme that she described is a 70-90 kDa glycoprotein with an isoelectric point of pH 5.5, optimum pH of 4.0, is stimulated by Ca2+ ions, but is inhibited by Fe3+ ions as well as palmitoylcarnitine.

P.D. Zuccolotto has adapted differential display to the study of *C. neoformans* by analyzing RNA from infected rat lungs. A major hurdle was overcoming the presence of contaminating rat RNA in their preparations. This was done by using a ficoll gradient as well as collagenase and SDS treatment to remove rat tissue thereby eliminating contaminating RNA. To date they have isolated six clones and are in the process of assessing their roles in virulence.

John Perfect has conducted research in a related area of differential gene expression during *C. neoformans* infections using rabbit and mouse models of infection. He has identified a number of genes which are expressed *in vivo* including cytochrome C oxidase subunit 1 (*COX1*), alcohol dehydrogenase (*ADH1*), and isocitrate lyase (*ICL1*). Perfect made the very important point that during his studies he has found that gene expression can vary depending on the model host used during infection. The last talk of this session was given by Gary Cox who is developing a model for antisense repression in *C. neoformans*. He has employed an inducible promoter to produce antisense transcripts of two well characterized genes, laccase (*CNLAC1*) and calcineurin A (*CNA1*). For each of these genes he has shown that their levels of expression can be reduced by antisense production.

The second molecular biology and biochemistry session occurred at the end of the week and included 9 talks. The first talk was given by Itzhack Polacheck who found that *C. neoformans* is sensitive to Nikkomycin Z although the inhibition was removed if there was ammonia or amino acids in the growth medium. Since Nikkomycin Z is an inhibitor of chitin synthases, the gene for chitin synthase was cloned and characterized. Future studies will investigate the role that this gene, *CHS1*, plays in susceptibity towards chitin synthase inhibitors. In the next talk, Elizabeth Wills described an essential gene in *C. neoformans*, phosphomannose isomerase (*PMI7*). This gene was disrupted and found to be essential for growth as the disruptants were not viable on media devoid of mannose. *Pmi7* mutants were found to be avirulent when tested in mice and were rapidly cleared from rabbitt CSF.

Ashok Varma described a useful molecular tool for studying *C. neoformans*. He has developed a dominant marker based on resistance to cycloheximide. The marker is an allele of the ribosomal protein L41 which was isolated from a UV-induced cycloheximide mutant by PCR. The gene encodes a small protein of 107 amino acids and can be used to transform wild type isolates to cycloheximide resistance. Sudha Chaturvedi described the isolation of a Cu, Zn superoxide dismutase (SOD) for the purpose of investigating whether there was a difference in this enzyme in the two varieties of *C. neoformans*. The rationale for this study was that while the *neoformans* variety primarily infects immunocompromised individuals, the *gattii* variety infects healthy people. The *neoformans* gene was isolated by complementing a *Saccharomyces cerevisiae sod1* mutant and then used to recover the *gattii* homolog from a genomic library. Comparison of the two *neoformans* genes revealed that there is a difference in the predicted shape and antigenicity of the two proteins. Studies are now underway to determine how mutants in this gene affect virulence.

Eric Jacobson is in the process of exploring the role of iron in the virulence of *C. neoformans*. Two mutants were isolated which were sensitive to hyperbaric oxygen. *Oxy1* mutants were normal for melanin production but defective for repression of ferric reductase while *oxy2* mutants were defective in melanin production but not ferric reductase activity. The *oxy1* and *oxy1oxy2* mutants were tested for virulence in mice and found to be reduced in virulence. It was hypothesized that the *OXY1* gene could be a homolog of the *S. cerevisiae* activator of ferrous transport gene (*AFT1*) while the *OXY2* gene could be a homolog of the metal binding activator gene (*MAC1*) in *S. cerevisiae*.

G. Blakely discussed some unique features of elongation factor 3 (EF-3) in *C. neoformans*. EF-3 is involved in protein translation and in fungi, may provide unique opportunities for antifungal drug design. The *C. neoformans* EF-3 gene is encoded by a 3168 bp transcript with a predicted protein of 1056 amino acids. The calculated molecular mass of this protein is 116.3 kDa. The *C. neoformans* gene shows only modest identity to the *S. cerevisiae* homolog and does not complement *S. cerevisiae* mutants. The *C. neoformans* gene may associate with ribosomes by a unique set of interactions as it was not possible to dissociate the protein from ribosomes using standard techniques. These results may suggest that the *C. neoformans* EF-3 gene may have properties unique from other fungal homologs.

Additional basic molecular biology studies were conducted on the *CNLAC1* promoter by Peter Williamson. In his talk, Williamson described the characterization of regions within the promoter which play a role in regulating melanin production. In addition to the consensus CAAT and TATA boxes, consensus Sp1 and E2F sites were observed which are typically found in higher eukaryotes. Surprisingly, *CNLAC1* expression was less at 37°C than at 25°C in spite of the fact that *CNLAC1* is required for virulence.

Jennifer Lodge has developed a way to apply signature tagged mutagenesis to *C. neoformans* for the purpose of identifying genes involved in virulence. A selectable marker was prepared in which unique tags could be attached and then integrated into the genome after transformation. In mixing experiments, it was found that each unique tag can be easily distinguished from other tags in mixed populations of up to 100 organisms. Preliminary data show that after passage through mice, some individual transformants are recovered in numbers less than others in the inoculum suggesting that these strains may be mutants reduced in virulence.

Massimo Cogliati has applied PCR fingerprinting to *C. neoformans* and concluded that in some cases, heterozygotes suggestive of diploids were identified. Methods for data analysis have been automated so that this technique can be used to screen large numbers of isolates in order to differentiate serotypes.

Tamara Doering investigated the structure of a major capsule component, glucuronoxylomannan (GXM) in order to begin to understand the steps involved in capsule biosynthesis. She found a novel mannosyl transferase whose activity is dependent on a number of factors including temperature, divalent cations, and substrate. When a collection of acapsular mutants was surveyed for mannosyl transferase activity, all were defective suggesting that this enzyme is important for capsule biosynthesis and, therefore, virulence.

In addition to the invited and free talks, there were a number of posters presented which covered diverse areas in molecular biology and biochemistry. There were two posters describing new molecular tools. Latouche et al. described a transformation system for *C. neoformans* var. *gattii* and McDade et al. described a dominant transformation marker (nourseothricin) based on the N-acetyltransferase gene of *Streptomyces noursei*.

Three posters presented data on the calcineurin signal transduction pathway (Görlach et al., Sia et al., and Cruz et al.) and three posters were on phospholipase B (Latouche et al., Santangelo et al., and Vidotto et al.). Halliday et al. presented data on variety *gattii* mating types in which they showed that in contrast to the *neoformans* variety, the ratio of *MATalpha* to *MATa* can approach 1:1 in *gattii* environmental isolates. R. Davidson et al. presented a poster on the mating signaling cascade while Cogliati et al. and Ohkusu et al. suggested that *C. neoformans* may be able to exist as a diploid. Cruz et al. presented data on rapamycin while Rodrigues et al. showed that *C. neoformans* can cleave fibronectin.

Epidemiological data were presented by Cogliati et al. who showed that $(GACA)_4$ primers were diagnostically useful and discriminatory for a number of different genotypes. A method for direct sequencing of the products from these reactions was presented by Allaria et al.

Posters on potential virulence factors of *C. neoformans* were presented by Chaudhry et al. (superoxide dismutase), Nyhus et al. (the *OXY2* gene), Kucsera et al. (*in vitro* encapsulation), Rosas et al. (melanization of *C. neoformans*), and Wright et al. (toxicity of *C. neoformans* metabolites). Vasilyeva et al. presented data on plant sources of melanin substrates for diagnostic media and Preziosi et al. used differential display to compare gene expression in two strains of *C. neoformans*.

Brian Wickes

chaired by
John Bennett and Tania Sorrell (II)
and Roderick Hay and Françoise Dromer (V)

Session II & V

Clinical perspectives Drugs and therapy

Presentations on the epidemiology, clinical features and management of cryptococcal infections, included data from patients in Australia and New Zealand, Papua New Guinea, Columbia, South Africa, The Netherlands, France, Japan and the United States, with most studies extending for a varying number of years up until 1996 to 1998. Interesting, but not unexpected, geographical differences were revealed. Changes in the incidence of infection paralleled the AIDS epidemic. The reports from Australia, The Netherlands and France, confirmed a fall in cases associated with the introduction of effective anti-AIDS therapies. In South Africa virtually all cases, where risk factors were known, were associated with HIV, compared with 77% in Columbia and The Netherlands, 44% in Australia and virtually none

Tania Sorrell

in Papua New Guinea. Amongst non-HIV infected patients in the USA, 82% were immunosuppressed. Only in Papua New Guinea, Australia, Columbia and South Africa were infections due to *Cryptococcus neoformans* var. *gattii* reported. In Australia and Columbia, there was a close association with non-immunocompromised hosts. It was of interest that in South Africa, although only 2.6% of isolates were due to *C. neoformans* var. *gattii*, 90% of them occurred in HIV-infected patients. Molecular studies confirmed that micro-evolution occurs in *C. neoformans* var. *neoformans* and, in response to drug exposure *in vitro*, in *C. neoformans* var. *gattii*. Dea Garcia-Hermoso presented interesting molecular epidemiological data suggesting that cryptococcosis may present many years after acquisition of initial infection, supporting the notion that reactivation of a latent infection accounts for at least some cases.

Clinical features were as expected, with the majority of normal hosts presenting with lung disease and immunocompromised hosts (particularly those with AIDS) with meningitis. An increased incidence of pulmonary cryptococcomas in patients infected with *C. neoformans* var. *gattii* infection was noted in Australia. In Papua New Guinea, the previously reported prominence of visual disturbance (noted in 53% of survivors) was confirmed and supported by the Columbian study. In Papua New Guinea, visual loss was associated with papilloedema and predicted by the development of an abducens nerve palsy and high CSF cryptococcal antigen titres. The possibility that corticosteroid therapy prevents visual deterioration was raised but not proven. Pulmonary cryptococcosis is the commonest form of the disease in Japan, where meningitis is rare, presumed to be due to a limited number of HIV infected patients in Japan. Pulmonary CT scans revealed multiple, cavitating, lesions. Tania Sorrell reported on a new approach to the non-invasive diagnosis of cerebral cryptococcomas, namely, *in vivo* magnetic resonance spectroscopy. Potentially diagnostic resonances arising from the cytosolic disaccharide, trehalose, were present in cryptococci cultured *in vitro* and in biopsy specimens from an animal model of cerebral cryptococcoma. Since cerebral mass lesions are found in up to 14% of normal hosts with cerebral cryptococcosis in Australia, this is a potentially important advance in diagnosis, which may avoid the need for a neurosurgical biopsy. Overall, mortality from cryptococcosis varied, being relatively higher in the developing countries (34%-40%, compared with 15% for neurological disease in the US study).

Bill Powderly reviewed studies of amphotericin B plus flucytosine, followed by consolidation therapy with fluconazole 400 mg per day, the use of azoles as single agents, introduction of lipid formulations of amphotericin and use of high doses of fluconazole (up to 2 grams per day) in combination regimes. Many of these studies involved small numbers of patients. He cautioned that cryptococcosis still has an acute mortality of at least 5%. In large prospective trials, mortality in patients in whom initial control of infection was inadequate, was as high as 20%. Early management of raised intracranial pressure, an important predictor of mortality, by measures including CSF drainage, placement of a ventricular peritoneal shunt, steroids and medical therapies was discussed. Powderly pointed out that there had been no controlled trials to indicate that lowering CSF pressure improves outcome.

The theme of drugs and therapy was taken up in another session, where experimental and newer dosage regimens of established agents were discussed. Enhancement of the immune response by combining anticapsular antibody with conventional antifungal agents or chloroquine appear promising in pre-clinical studies. There was debate about the proposed dose escalation trial of anticapsular antibody and appropriate clinical end points. The observation that this antibody improves opsonization and elimination of capsular polysaccharide from serum and tissues is potentially attractive for therapy. In combination with chloroquine, (which exerts its anti-cryptococcal effect by raising pH in lysosomes), anticapsular antibody enhanced the anticryptococcal activity of human monocyte-derived macrophages and prolonged survival in an immunocompetent mouse model of intravenous infection. John Graybill summarised *in vivo* experience with new compounds in the treatment of cryptococcal meningitis and new drug combinations. Many data were preliminary. In acute animal models (not reminiscent of human infection), immune stimulation with IL-12 or G-CSF in combination with conventional antifungal therapies was beneficial. In a mouse model, triple therapy with conventional antifungal drugs amphotericin B, fluconazole and flucytosine was more effective than single or two drug combinations. Bob Larsen reviewed data on the combination of fluconazole plus flucytosine, with escalating fluconazole doses of up to 800 to 2000 mg per day. He presented some evidence that the combination was of superior efficacy, with response rates greater than 80% when doses of fluconazole were at least to 1200 mg daily. He referred to a previous report of triple therapy (AMB, flucytosine and fluconazole) in human cryptococcal meningitis, in which 38/42 (81%) patients survived after 10 weeks of therapy. Sterilization of the CSF within two weeks, was associated with an improved response. The Japanese group reported that fluconazole, 400 mg daily, was effective in the treatment of pulmonary cryptococcosis. A novel lipid nanosphere-encapsulated amphotericin B, NS-718, was reported by the same group to show efficacy against murine pulmonary cryptococcosis. The nephrotoxicity of this drug was less than that of conventional amphotericin B in a rat infusion model.

A round-table discussion entitled «Controversies in cryptococcosis» was chaired by John Bennett. The proposition that flucytosine no longer has a role in the treatment of cryptococcosis was debated in the context of published clinical data. Though inconclusive, largely because of incompleteness of data sets, it was agreed that amphotericin B in combination with flucytosine remains the initial treatment of choice in HIV-negative patients with CNS cryptococcosis and in moderate to severe cases in HIV-infected patients. There was disagreement amongst panellists about the value of monitoring serum levels of flucytosine.

There was little evidence of emerging resistance to *C. neoformans* in the clinical setting, although in a Spanish study about 3% of isolates had a MIC to fluconazole of at least 64 mg per litre when determined by the NCCLS microdilution reference method. MICs90 of 2 mg/L (fluconazole) and 0.25 mg/L (terbinafine) were reported in a large Australian study. Another poster from the Spanish group indicated that none of 128 clinical isolates from different regions of Spain demonstrated resistance to amphotericin B *in vitro* and all isolates had MICs to voriconazole of <1mg/L.

Tania Sorrell

chaired by
S.M. Lewitz and Christopher Mody (III)
and Juneann Murphy and Arturo Casadevall (IV)

Session III & IV

Pathogenesis and host responses

The second day of the Conference was dedicated to the intriguing issue of pathogenesis and immune response in cryptococcosis. The variety of issues presented that day prompted me to identify a simplistic but likely helpful scheme. I will describe my take-home lessons accordingly:

1) pathogen-specific moieties: a) offence devices and b) antigenically relevant structures;

2) host-specific reactions: a) antibody response, b) cytokine network and c) effector systems and their cross-talk via cell surface adhesion molecules.

David Goldman described the phenomenon of phenotype switching in *Cryptococcus neoformans*. Already well known in other microorganisms (*Candida albicans, Neisseria meningitidis, Haemophilus influenzae*), such phenomenon also occurred in cryptococci, where switching was relatively frequent ($10^{-3} - 10^{-4}$), produced different types of colonies (smooth, wrinkled, pseudohyphal, serrated) and resulted in diverse degrees of virulence in the mouse model. Not only morphology and virulence were affected but also the type and intensity of immune reaction evoked in the infected mice differed among different switching-derived colonies.


Elisabetta Blasi

By comparing two clinical isolates of *C. neoformans*, that differed in phospholypase B (PLB) production, C.J. Clancy showed that both *in vivo* (mouse model of intranasal infection) and *in vitro* (endothelial and phagocyte infection models) the PLB producer isolate had a higher degree of virulence when compared to the non producer counterpart. Interestingly, the most deleterious effects of PLB were observed in terms of pathogenetic effects *in vivo* (enhanced fungal burden, inflammatory reaction, parenchymal damage) as well as better adherence and enhanced damage of host cells *in vitro*.

Ultrastructural studies on lung tissues from infected mice (Marta Feldmesser) depicted the complexity of the pathogenetic events occurring at the intracellular level. Particularly, intramacrophagic budding of *C. neoformans* was documented, thus implying that this fungus might be listed among the facultative intracellular pathogens. Moreover, by golden labelling data, suggestive evidence was provided on a novel role for a capsular polymer, glucuronoxylomann (GXM), as a causative agent of disordered recycling and development of lysosomes within macrophages, in turn, resulting in affected intracellular defense devices.

According to immunological findings, molecular and biochemical approaches were prompted by S.M. Levitz and by Carmelo Biondo to identify cryptococcal proteins capa-

ble of evoking relevant T-cell response(s), that might become potential candidates for the design of a new vaccine. From these studies the list of possibly useful proteins certainly grew. Novel insights were also provided on the multiple stimulating roles of such antigens, particularly the novel mitogenic potential described by Christopher Mody.

On the other hand, Matthew Scharff's contribution originated from the knowledge that some mouse monoclonal antibodies directed to the capsular polysaccharide GXM were in fact protective. Thus, a flash was given on the complexity of the approach as to choose and synthesize the most appropriate peptides that by mimicking a given cryptococcal moiety (polysaccharide) might be useful for eliciting a protective antibody response. Also in these studies the ultimate aim was to provide a new tool for successful anticryptococcal vaccination protocols.

Liise-Anne Pirofski showed a wide spectrum analysis aimed at investigating the meaning of antibody response against *C. neoformans*. Isotype and idiotype restriction were documented in human anticryptococcal antibody repertoire and even more specific differences appeared by comparing HIV- and HIV+ patients, adults and children. The overall message was that resistance and susceptibility to cryptococcosis in those patients correlated with qualitative and quantitative differences in the antibody repertoire (anti-GXM antibodies, V_H3 depletion). The multistep complexity of mechanisms mediating antibody-dependent protection was underlined by the finding from David Beenhouwer. Using an experimental model of cryptococcosis in gene disrupted mice (IL-4 and IL-10 knock out mice), he demonstrated that when therapy was attempted by administration of exogenous anti-GXM antibodies a crucial contribution came from the host immune cell system. In particular, a TH2-type response was required to set-up successful protocols for antibody therapy against cryptococcosis.

The relevance of anti-capsular antibodies in host protection was linked to the epitope specificity that in turn influenced activation and binding of C3 fragment to cryptococcal capsule. An elegant demonstration of epitope distribution on *C. neoformans* came from differential interference contrast (DIC) microscopy studies presented by Thomas Kozel that showed two diverse pictures (rim versus puffy) of antibody-treated cryptococci when different strains were investigated. The message was that host-pathogen interaction strictly depended on both antibody specificity and epitope localization within microbial external structures (capsule).

Insights on the biomolecular aspects of immune reaction to *C. neoformans* were provided by means of *in vivo* and *ex vivo* infection models. Gary Huffnagle provided extensive evidence and fascinating models describing putative mechanisms for lung resistance/susceptibility to cryptococcosis. An integrated network of cytokine signaling and cellular recruitment/action was proposed. In particular, the production of TH1- over a TH2-type cytokine was crucial for establishment of protective immune response as well as the involvement of CC chemokines (MIP-1α, MCP-1) for leukocyte recruitment.

Furthermore, Tim Traynor provided definitive evidence that an appropriate Th1-type reaction was strictly dependent upon the expression of CCR2, the primary receptor for MCP-1, namely upon an intact cytokine/cytokine receptor system that allowed recruitment of macrophages and $CD8^+$ T cells. Karen Aguirre provided insights on the mechanisms of $CD8^+$ T-cell-related resistance to *C. neoformans*. By transfer experiments employing specific cell subsets and conventional versus gene disrupted mice, she showed that $CD8^+$ T cells, in fact, mediated resistance to cryptococcosis provided that also $CD4^+$ T cells were present. Kinetically, $CD8^+$ T-cell recruitment preceded influx of $CD4^+$ T cells at least in the infected lungs.

Satomi Yara looked at dissemination of *C. neoformans* from the lung to the cerebral district and focused on β2 integrin family adhesion molecules. The major finding indicated that, although not involved in the control of fungal load in the lung, CD11b (Mac-1) molecule appeared essential in allowing dissemination through the blood to the brain. Another important message provided was that no direct correlation occurred in the number of microorganisms detected in the lung and in the blood or in the brain compartment, thus implying different peculiarities among anatomical sites in handling microbial infections.

Kazuyoshi Kawakami expanded his recently published *in vitro* studies on cytokine network during cryptococcosis by providing extensive and convincing evidence that also *in vivo* IL-18 collaborated with IL-12 in inducing IFN-γ, the clue cytokine in anticryptococcal defenses, known to promote protective response.

By comparative studies in gene disrupted mice ($IL\text{-}12p40^{-/-}$ versus $IL\text{-}12p35^{-/-}$ knock out mice), Gottfried Alber documented the expected Th2 polarization in such knock out mice and, more strikingly, observed a higher susceptibility to *C. neoformans* in $IL\text{-}12p40^{-/-}$ mice with respect to the $IL\text{-}12p35^{-/-}$ counterpart, pointing to a novel protective role of IL-12p40, independent on its well established involvement in the formation of p75 heterodimer.

Juneann Murphy's and Anna Vecchiarelli's contributions ascribed to specific host surface molecules (CTLA-4 and CD68, respectively) precious co-regulatory roles in the cross-talk between the diverse immune components, thus affecting the outcome of the immune reaction. In particular, CTLA-4 had a negative role since anti CTLA-4 antibodies resulted in the correct development of a protective immune response, while CD40/CD40L interaction was required and critical for the accomplishment of both secretory (proinflammatory cytokine production) and effector (anticryptococcal activity) functions by human monocytes.

Overall, the presentations and the discussions occurring within that second day of the meeting significantly contributed from different points of view to our understanding of host-pathogen interaction during cryptococcosis. Elisabetta Blasi showed that *C. neoformans* isolates, serially obtained from an AIDS patient at different times of his clinical history of recurrent cryptococcosis, were identical in electrokaryotype, thus implying the occurrence of relapses. Furthermore, similarities but no cases of identities were observed by assessing the same isolates by RAPD and ddPCR. Differences were also evidenced in the way such isolates interacted with host immune cells *in vitro*, in particular, in their susceptibility to phagocytosis and killing as well as in their ability to evoke a secretory response by the phagocytic cells. Thus, by correlating genotypical and phenotypical differences, these findings underlined an intriguing issue, arguing on the putative importance of cryptococcal plasticity or "microevolution", as recently defined by the literature, in the pathogenesis of cryptococcosis and particularly in fungal persistence and relapses.

Elisabetta Blasi

chaired by
David Ellis and June Kwon-Chung

Session VI

Epidemiology/Ecology/Evolution

It gives me great pleasure to report on both the ecological and epidemiological aspects of the 4th International Conference on Cryptococcus and Cryptococcosis. This was a stimulating scientific meeting which reflected the advances in knowledge of this fungus. It was a credit to the scientific organising committee to exhibit such a broad spectrum of new material.

Of ecological interest to the cryptococcal world there have been a number of groups investigating the natural habitat of *Cryptococcus neoformans* var. *gattii*, particularly in South America. I was very interested in Elizabeth Castañeda's group who have isolated serotype C from almond trees in Colombia. In order to study the host-fungus interaction and to establish survival of the fungus in the trees, almond seedlings were inoculated and then 4 weeks later the authors were able to demonstrate the yeast growing in the pith of the seedlings. The Brazilian group led by Marcia Lazera has also isolated serotype A from 2 different shower tree species as well as fig trees. It is of great interest to note that this group also found serotype A and B coexisting in the same hollow in two of the pink shower trees. It would appear that wood is becoming an increasingly important ecological habitat for *C. neoformans* that warrants further investigation.

Tania Pfeiffer

Epidemiologically, Françoise Dromer's group presented data from a French survey of cryptococcosis dating back from 1985. This is an ongoing survey aiming to evaluate the influence of various parameters on prognosis. One particularly interesting outcome of Dromer's study is that the median time between the onset and the diagnosis of cryptococcosis was significantly shorter for AIDS patients (2 weeks [1 day - 16 weeks] compared with 3.5 weeks for non-AIDS patients [1 day - 62 weeks], $p>0.05$).

Gianluigi Cardinali and a group of Milano have been working on computer-aided systems for the evaluation of DNA banding patterns from *C. neoformans*. Their work involved a multicentre comparison of two already existing systems with the one they are developing in their laboratories to analyse the clustering of strains.

A group at the CBS Yeast Division headed by Teun Boekhout performed an extensive world-wide comparison of environmental and clinical isolates of both *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii* using a variety of molecular techniques. The outcomes of their research have led to a series of questions regarding the evolution of cryptococcal populations. Boekhout hypothesised that the unbalanced population structure of the pathogen may be due to the rapid colonization of a niche or habitat by a few well adapted genetic lineages after that niche or habitat has become available. Alternatively, the presence of many rare genotypes may provide a reservoir for future selection of particular genotypes.

Molecular epidemiology was discussed by Wieland Meyer et al. who used several different techniques including PCR and RAPD analysis to evaluate over 400 global isolates of *C. neoformans* - both varieties. The analysis separated the isolates into 8 major groups, and the results indicated a possible association with human population migration. Interestingly, the Australian *C. neoformans* var. *gattii* isolates showed that regional profiles of eucalypt-derived and clinical isolates were concordant, supporting the epidemiological association of the red gums and human infection. June Kwon-Chung made the closing presentation for the day posing the interesting question as to whether C. neoformans is evolving into an asexual organism. All C. neoformans var. neoformans serotype A isolates, both clinical and environmental, have been of the alpha mating (MATa) type. Kwon-Chung has been unable to find neither a naturally occurring "a" type or to create a MATa by genetic crossing between MATa (serotype A) and MATa (serotype D).

A round table discussion on the final day of the meeting stimulated much academic debate over changing the name of *C. neoformans* var. *neoformans*, serotype A to *C. neoformans* var. *grubii*. Ira Salkin, Weiland Meyer and Arturo Casadevall presented genotypic evidence to support the renaming of the varietal type, whilst June Kwon-Chung argued against the proposed name change until we understand the genetic basis of serotype determination and come up with simple laboratory test which can be used to distinguish between the two var. *neoformans* serotypes. Hence, as far as clinical laboratories are concerned the var. *grubii* name change at this time point is not only an academic issue but also will prematurely create confusion in literature. For instance, if we base the serotyping data for distinction between var. *grubii* vs. var. *neoformans*, what should we call those strains of AD serotype?

In my opinion one of the most interesting discussions of the meeting revolved around the debate of serotype versus genotype in cases where the results do not correspond. Casadevall made a pertinent comment that genotypic characterization is more important because serotyping is «just how a bunny sees *Cryptococcus neoformans*». The issue of the name change to var. *grubii* was obviously of great interest to everyone at the meeting and I am sure it will be further discussed at the 5th ICCC Adelaide meeting in 2002 where there will undoubtedly be more evidence to support the debate.

Tania Pfeiffer

Impressions of TIFI5

by Peter Donnelly

The weather was beautiful, the delegates, nicely dressed with their pristine badges and conference bags swarmed into the Conference centre. The posters were in place, the exhibition was attractive and not overdone and there was almost a buzz of anticipation. At 14:00 precisely, with the Republic hall packed almost to capacity the President greeted everyone and formally opened the meeting. The first session got underway with each speaker doing his utmost to set out the size and nature of the problem of nosocomial fungal infections. «Candida is the fourth most frequent cause of bloodstream infections in the USA» (I, for one find the term "bloodstream infections" a misnomer and inaccurate since none of the common causes of so-called BSI actually causes infections of the bloodstream per se but why quibble). It was confirmed again that the risk factors for yeast infections were practically everything done in Intensive Care, transplantation and the treatment of haematological disease. These same medical ambitions are also still being thwarted by that worst nightmare, aspergillosis. That this fungus has become the Prince of Opportunistic Pathogens is not really surprising since the fungus is quite literally to be found everywhere. Even the ubiquitous kiwi fruit is a haven for the saprophyte.

To listen to almost every speaker, one would think that the small island was being besieged by a mycotic plague but then this is understandable given the nature of the conference. The observant and those more interested in touristy things will have noticed that the conference centre was once home to the Knights Hospitallier, the Knights of St John, who ran the Sacra Infermeria from 1574 onwards. Unlike modern hospitals which go upwards and tend to resemble a theme parks or corporate headquarters, this infirmary or hospital extended downwards into the bowels of the earth. Incredibly, it had 544 beds and provided care for all the residents of Malta and Goza confronted by the misery wrought by the four horsemen of the Apocalypse; the plague in 1674, the pestilence of Malta fever 200 years later, the countless victims of armed conflict (and there were many centred round this fortress island) and the emaciated in times of famine both natural and man-made. The physicians and surgeons were expert in removing bladder stones (record 2.54 minutes without anaesthetics) and cataracts. Whether they knew anything of fungal diseases is uncertain but they certainly knew enough about contagions to react swiftly and decisively by enacting strict if sometimes draconian measure to minimise the risk of spread. This approach to the control of fungal infection would certainly have appealed to some members of the audience.

One of the primary objectives of TIFI is to offer an educational forum for experienced clinicians from various disciplines and microbiologists who have to manage patients with fungal infection. The session on defining fungal infectious disease couldn't have been better chosen but was poorly attended. This is surprising given the degree of dissatisfaction and frank confusion amongst clinicians and researchers alike in diagnosing fungal disease. The organisers might have foreseen this and placed the session in the morning giving it the pride of place it deserved. Those participants who are now used to treating empirically and have learned to do without laboratory diagnosis would have been surprised to find that the backroom boys and girls have come out of the closet and are claiming to be a useful, even necessary, part of the team. The mycologist affirmed he was indispensable in identifying the cause of mycosis, the radiologist is no longer shy about interpreting a variety of pulmonary and other abnormalities and even showed how his art could help obtain direct the collection of appropriate specimens. The mysteries of PCR and microbial product detection were revealed and shown to provide practical and reasonable mycological evidence. But I fear the clinicians were not impressed since these tests 'lacked specificity". Even if the negative predictive value of a test approached 100% many would still not find the results credible enough for them to stay their hand against treating empirically. This would suggest there is much to be done in order to assuage this crisis of confidence in the laboratory.

The case reports were not a great success partly because the setting was not conducive and the audience was inhibited from participating - they were, after all in a theatre watching the stage where the action took place. Moreover, although presenters always get miffed when told how to present, I had the distinct feeling that none was given much guidance on what was expected of them. By contrast, the posters were colourful and there were more than I had expected. One particular example from Brazil would have won my vote for first prize (had there been one) for its elegant simplicity as it had a clear objective, exemplified the scientific method, presented the data clearly and actually succeeded in delivering results which needed no

statistics to strengthen the case. But then the subject was straightforward.

There were few trends to observe except that the grey and the good had given way to youth, not always a wise decision as the quality of lectures wavered and was sometimes quite frankly below par. The choice of topics looked tasty enough but what was delivered was sometimes as cold and dull as one or two of the meals we had at recommended restaurants. Still I did learn that when sexually active, *Candida lusitaniae* goes about dressed up as *Clavispora lusitaniae*. I also learned that amphotericin B becomes innocuous if you heat it at 70°C before administering it without apparently losing any of its antifungal activity. I can only guess at what inspired this observation but its almost culinary nature should have suggested it's French origins. I also heard that patients actually enjoy the visual disturbance and photosensitivity induced by voriconazole (perhaps reminding them of their erstwhile youth in the psychedelic Sixties!). What I still didn't learn was how much drug should be administered to treat fungal infection and for how long. These studies have never been done and may now never be done.

At the Gala dinner guests were greeted by what appeared to be the Knights of St John, a trumpet and a welcome glass of cool champagne. Then we all trooped downstairs to the long room which had once been a ward and took allotted seat. The Grand Master entered with due pomp and ceremony and invited all to spread their hands as if in greeting. Then he sang the Pater Noster in Latin, which neatly circumvented the usual embarrassment at saying grace before the meal. The meal was hale and hearty and spirits were high with everyone clearly enjoying himself or herself.

During a lull between courses I had time to muse over a few other aspects of the meeting. TIFI managed to attract representatives from 37 countries across the globe making it a truly international meeting. Numerically the Italians

comprised the largest contingent followed by the Brits but gratifyingly the two attendees from Malta made sure the host country had the best attendance rate per million inhabitants. The smaller countries of Europe particularly Finland, Belgium, the Netherlands and Portugal also had a strong presence. By contrast, North America was all but absent with only 18 delegates from the USA and 5 from Canada. Yet, the American brand of the English language had clearly left its mark. For instance, the phrase "level of anxiety" was used to justify the empirical approach to therapy that considers diagnosis an unnecessary encumbrance and hindrance to the hustle and bustle of a busy haematological ward. The term "emerging" has taken on an entirely new meaning and seemed to have been chosen more as an attempt to breath new life into dusty old topics than convey the idea that something new is afoot. Besides, I am used to people emerging out of the mist, monsters emerging out of the swamp and ghosts emerging out of graves. Might this image have led Merck to name its echinocandin MK-00991 Caspofungin? Bristol Myers Squibb are clearly excited about their azole having christened it RAVuconazole but the thinking behind Schering Plough naming their SCH 56592 POSAconazole quite frankly leaves me baffled. Did they really think that people like me could resist the temptation to make an irreverent quip that the drug might not be a genuine new antifungal but simply posing as one? Still, I am grateful since I can now add new names to the Conazole family - with Mike, Katy, Flo, Ytra and Furry now being joined by RAVER and POSER!

Every event has its zenith and nadir and this conference was no exception. The hapless doctor who presented the first case clearly had different ideas from is audience. The slide projector continued to exercise autonomy cutting out completely or skipping a few slides at random to the consternation and irritation of speaker and audience alike. Some of the less experienced (and one or two of the more experienced who might have known better) seemed unable to distinguish between getting the message across and delivering a litany of detail. «We perhaps have room for one question» almost became a catch phrase and caused considerable mirth amongst the audience when the chairperson more than once took the opportunity to ask the one and only question. Curiously the speakers seemed to gone native, perhaps seduced by the Mediterranean climate and tempo of Malta and wilfully paid no heed to their time limit.

All in all the conference was worthwhile and there was time to learn at least something new and to explore a little more than might have been expected. Ideas were certainly shared. But updating of knowledge was not really very likely given that many delegates were fresh from ICAAC. Never the less, hearing the experts view's are the same as one's own is also reassuring and confirms that one is up to date. Old friends were greeted and new ones made but whether TIFI5 was as lively and fascinating, as the organisers wished must be left up to each and every delegate to decide. I enjoyed it anyway. Doubtless those who attended conscientiously will have found some of the intended gems. However, the silent city and other sights and sounds of Malta clearly proved too much to resist for many of the delegates who had better things to do especially as the weather was finer than expected.

Barcelona 2000:
the 6th Congress of the ECMM

(continued from page 5)

as Dr. M. Pereiro-Miguens (ex-President of the AEM), J. Vilanova, C. Ramirez, and others have devoted part of their lives to the study of the fungi and diseases they cause. There are currently various centres throughout Spain, particularly at Universities, where professional doctors, veterinarians, pharmacists and biologists develop their activities. There are research groups in taxonomy, epidemiology, immunology, genetics, diagnosis and treatment which are deserving of national and international recognition.

The AEM has played and intends to play a major role in the development of Mycology. The «Revista Iberica de Micología» (Iberian Mycology Journal) was founded in 1984 and transformed in 1990 into the «Revista Iberoamericana de Micología» (Ibero American Mycology Journal). This is the official organ of the AEM and of the Brazilian Society of Mycology. After 15 years of uninterrupted publications it has managed to occupy its place in the international scientific press; this Journal will publish the abstracts of the 6th Congress.

All sessions of the Congress will be held in the elegant Barcelona Hilton Hotel, located on the central and distinguished Avenida Diagonal. It has all the modern conveniences for the participants to feel comfortable both in their rooms and at the scientific events. For those who prefer different accommodation, less expensive hotels are available that also provide comfortable surroundings. The social events, starting with the Gala dinner, are accessible to all the participants.

The Organizing Committee, always in agreement with the Council and the National Societies of the ECMM, proposes a topical and attractive scientific program, that seeks to discuss subjects that are the principal challenge of the 21st century: these include changes in epidemiology of mycoses in the new era of antiretroviral therapeutics; the importance of fungal infections in critical non-neutropenic patients; hospital infections and how to determine and control them; the importance of molecular biology tests in fungal taxonomy, as a method of diagnosis, and in defining more precisely the epidemiology of mycoses. The important migratory flows and the movement of millions of people to countries where there are endemic mycoses, mean that in Europe imported mycoses are becoming increasingly frequent. This will be the subject of one Round Table. Others will include pathologies caused by the new species of the *Malassezia* genus and the need for a consensus for the treatment of superficial mycoses. An outstanding opportunity and forum will be afforded to the presentation of the current data referring to the anti-fungal drugs and their clinical applications.

Among the challenges of the 21st century to be considered will be the future of specialized journals in Medical Mycology. The trend to publish in Microbiology journals offering a greater *impact factor*, and the possibility of new electronic publications can affect the existence of many of these journals. The situation will be analyzed at a Round Table and forum: *Medical Mycology Journals and the Challenge of the III Millennium*. This programme, structured and moderated by experts in the subjects, will include free papers chosen by the Scientific Committee for their originality and quality. Free communications in poster-form will be presented throughout the Congress and set up especially in the coffee-break areas, with a set time for the authors to discuss their results with the audience.

In conclusion, the aim of the next 6th Congress of the ECMM is to debate general problems of European scope and to promote participation, especially of the younger members, who can find answers to their questions or better still, new questions concerning new advances in Medical Mycology.

Interdisciplinary Forum on Aspergillosis

An international workshop on *Aspergillus* and Aspergillosis will be held from 7 to 8 April 2000 at the Department of Bacteriology, Institute of Hygiene, University of Göttingen, Germany.

The workshop will be supported by the Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM) and the Deutschsprachige Mykologische Gesellschaft (DMykG).

Most aspects of the pathogen and the disease will be covered in an interdisciplinary approach.

Applicants are referred to:
Prof.Dr. Uwe Gross
Hygiene Institut der Universität
Kreuzbergring 57
D-37075 Göttingen
Phone: +49-551-395806
Fax: +49-551-395861
E-mail: ugross@gwdg.de

Mycology Courses in Europe (2000)

BELGIUM

Course on Medical and Veterinary Mycology *(every year)*

Organizers: Proff. D. Swinne and I. Surmont
Address: Institute of Tropical Medicine, Nationalestr. 155, B-2000 Antwerpen, Fax +32 3 2161431
Duration - date: Four months (one full day/week) - March to June
Hours theory/practice: Theory 30h / practice 70h
Admitted participants: 20
Scientific programme: Morphology, classification, identification of filamentous fungi and yeasts. Superficial, subcutaneous and deep mycoses: clinical forms, etiology, ecology, epidemiology, diagnosis and treatment
Certificate: Diploma

BULGARIA

Course on Diagnosis of Systemic Mycoses

Organizer: Prof. T. Kantardjiev
Address: National Center of Infectious and Parasitic Diseases, 26, Yanko Sakazov Blvd., Sofia 1504
Duration - date: Eight days - May 1-5 and 8-12, 2000
Hours theory/practice: Theory 50h / practice 20h
Admitted participants: 10
Certificate: Diploma

FINLAND

Cours on Mould Identification

Organizers: Finnish Society for Medical Mycology & AEL
Address: AEL, Kaarnatie 4, FIN-00410, Helsinki. Information: <maija-liisa.kuusela@AEL.fi>
Duration - date: Three days - March 15-17, 2000
Hours theory/practice: Theory 8h / practice 10h
Admitted participants: 14
Certificate: Diploma

FRANCE

Cours de Mycologie Médicale *(every year)*

Organizers: Dr. Cl. de Bièvre (Director of the course), Dr. P. Boiron (Head of practical works)
Address: Institut Pasteur, 28 Rue du Dr. Roux, 75015 Paris, Fax +33 1 45688420
Duration - date: Eight weeks - April 25-June 13, 2000
Hours theory/practice: Theory 100h / practice 100h
Admitted participants: 20
Scientific programme: Clinical and mycological features of deep-seated and superficial mycoses. Diagnosis, treatment, identification
Certificate: Diploma Institut Pasteur and Université Paris VI Paris VII

GERMANY

Course on Clinical Mycology *(every year)*

Organizers: Prof. H. Bernhardt (Chairman), Dr. K. Tintelnot (Co-chairman)
Address: Working Group "Clinical Mycology" of DMykG, Fax +33 1 45688218
Duration - date: Two days - February 18-19, 2000
Hours theory/practice: Only theory
Admitted participants: 25
Scientific programme: Antimycotic susceptibility tests. Identification of yeasts. Immunological diagnostic of candidose opportunistes, Aspergillus

Germanspeaking CBS-Course: Estimation of fungi and yeasts

Organizers: G.S. de Hoog (Baarn, The Netherlands), M. Weig and D. Harmsen (Würzburg, Germany)
Address: Institut für Hygiene und Mikrobiologie der Universität Würzburg, Josef-Schneider-Str. 2, D-97080 Würzburg
Duration-date: 14 days - March 13-25, 2000
Hours theory/practice: Theory 35% / practice 65%
Admitted participants: 50
Scientific programme: Estimation of mould and yeasts, mycological laboratory methods including moleculare diagnostics
Certificate: Diploma

HUNGARY

Course on Diagnosis of Dermatomycoses

Organizers: National Institute for Dermato-venereology and Mycological Section of Hungarian Dermatological Society
Address: Maria Str. 41, H-1085 Budapest
Duration - date: Three days - January 26-28, 2000
Hours theory/practice: Theory 8h / practice 16h
Scientific programme: Biology of fungi; Medically important fungi; Epidemiology of mycoses; Laboratory techniques: microscopy, culture, identification, susceptibility testing
Certificate: Certificate

POLAND

Course on Dermatological Mycology *(every year)*

Organizers: Prof. R. Maleszka and others
Address: Oddzial Dermatologiczny Szpitala MSW, ul. Dojazd 34, 60-631 Poznan
Duration - date: Five days - September 5-9, 2000
Hours theory/practice: Theory 12h / practice 36h
Scientific programme: Dermatomycoses (description of the fungi, biology, clinical description, laboratory diagnosis, treatment)
Certificate: Certificate (after examination)

Advances in Mycologic Dermatology

Organizers: Prof. E. Baran and others
Address: Clinic of Dermatology, 50-368 Wroclaw, Chalubinskiego 1
Duration - date: Three days - March 27-29, 2000
Admitted participants: 10
Hours theory/practice: Theory 12h / practice 10h
Certificate: Diploma

SPAIN

Course on Medical Mycology *(every year)*

Organizer: Dr. Josep M. Torres-Rodríguez, Unitat de Microbiología, Institut Municipal D'Investigació Mèdica, C/ Aiguader 80, 08003 Barcelona, Fax +34 93 221 3237
Address: Departamento de Microbiología, Fac. Medicina "UDIMAS", Universidad Autònoma de Barcelona
Duration-date: Three weeks - February 2000
Hours theory/practice: Theory 65% / practice 35%
Admitted participants: 15
Certificate: Diploma

THE NETHERLANDS

Course Introduction to Systematic Mycology

Organizer: Centraalbureau voor Schimmelcultures, Baarn
Address: CBS, Oosterstr. 1, 3742 SK Baarn, Fax +31 3554 16142
Duration - date: Three weeks - March 13-30, 2000
Hours theory/practice: Theory 30h / practice 75h
Admitted participants: 20
Scientific programme: Classical mycology course on biodiversity and taxonomy including one day medical mycology
Certificate: Diploma

Repetitive two-days workshops on dermatophytes

Organizer: Centraalbureau voor Schimmelcultures, Baarn
Address: CBS, Oosterstr. 1, 3742 SK Baarn, Fax +31 3554 16142
Duration - date: Two days - 5 times/year
Admitted participants: 25
Certificate: Diploma

UNITED KINGDOM

Course on Identification of Pathogenic Fungi

Organizers: Dr. E.M. Johnson and Dr. C.K. Campbell
Address: PHLS Mycology Reference Laboratory, Bristol Public Health Laboratory, Kingsdown, Bristol BS2 8EL
Duration - date: Three days - July (date to be finalised)
Admitted participants: 50
Certificate: Diploma

(Information provided by the member Societies)