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 19 different countries)

2/98

ECMM
European Confederation of Medical Mycology

CEMM
Confédération Européenne de Mycologie Médicale

Message from the President

The fourth Congress of the ECMM was held in Glasgow (Scotland). This meeting was very successful. A large audience from Europe and countries outside Europe attended the sessions. The scientific program and the organisation were excellent. For the first time preliminary results of the epidemiological surveys on candidemia, cryptococcosis, histoplasmosis, tinea capitis and nocardiosis were presented. On behalf of ECMM members I extend warm thanks to Gillian Shankland, the local organizer, and the organizing committee: E.G.V. Evans, R. Hay, M. Richardson and E. Johnson for their commendable efforts.

Prof. E.G.V. Evans, President of ISHAM, and Prof. B. Dupont, President of ECMM, with Glasgow's Officials Dignitaries at the Civic Reception of the 4th ECMM Congress in Glasgow.

The ECMM Congresses have established themselves as amongst the most important scientific meetings of our discipline. They provide evidence for the continuing growth and assumed future of European mycology. Several European mycological societies are preparing the next congresses of the ECMM: the German society (President Prof. Hannelore Bernhardt) that will host the 5th Congress in Dresden from June 3 to 9, 1999; the Spanish Society will organize the 6th Congress in Barcelona, Spain, for the Autumn of 2000; the Israel Society has offered to host the 7th Congress in Tel Aviv in 2001; the Polish Society the 8th Congress in Poland in 2002, and the Netherland Society the 9th Congress in 2003. This level of commitment is really impressive.

The ECMM was very pleased to hear that Finland now has a society of medical mycology which is planning to join the ECMM. If approved by the Council, the Finnish Society would become the 20th member.

I take the opportunity of this message to thank Marianna Viviani once again for her exemplary efforts on behalf of the ECMM and to send to all of you my personal best wishes for the end of the year.

Bertrand Dupont

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National meeting: 2000, Poznan
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National meeting: April 20-21, 1999, Veldhoven

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National meeting: February 1999, Liège

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National meetings: May 21-22, 1999, Strasbourg; November 25-27, 1999, Paris
Journal: Journal de Mycologie Médicale

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Membership 1998: 105
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Turkish Microbiological Society Mycology Section
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Membership 1998: 21

(Information provided by the member Societies)

News from the French Society

The «Journal de Mycologie Médicale», published by the Société Française de Mycologie Médicale, has fixed a reduced rate for the 1999 subscription (4 issues) for the ECMM members: FF 579 instead of FF 1120.
Contact: Prof. Bertrand Dupont, Institut Pasteur, Unité de Mycologie, 25 rue du Docteur Roux, 75724 Paris, Cedex 15, France; fax +33 1 4568 8420.

Importance of the Quality Control in Mycology

In this issue Dr. Alain Leblanc, responsible for organization of the national Quality Control in France from 1979 to 1996 at the Laboratoire National de la Santé and afterwards at the Agence du Médicament, reports the experience in his country.
Future issues of the Mycology Newsletter will contain contributions from other countries, with a view to recording what has been and is being done at present throughout Europe. This information could then form the basis for future co-operative action.

The introduction of automation to clinical analysis laboratories that has occurred during the past decades has introduced modifications in their daily practice and called for the need for a quality control programme, comparable to those made by industry after the 2nd World War.

Since the end of the 1960s, interlaboratory controls have been organized here and there at national or regional level, first in biochemistry, and, soon thereafter, in the other branches of medical biology, mycology included.

Thus in France, since the beginning of the 1970s, and following the initiative of professional organisations, External Quality Assessment programmes have been proposed for laboratories of medical biology, including biochemistry, haematology, bacteriology, virology, and parasitology, to which, in France, mycology is associated.

Since 1979 the External Quality Assessment was been made mandatory by law for the 5000 French laboratories, public as well as private.

This External Quality Assessment, necessarily retrospective, could not be used to validate the daily results assessed by Internal Quality Control. The main aims of External Quality Assessment were to normalise the results, improve their quality, and acquaint biologists with the quality of their performance, thus promoting improvement through continuous training, quality control being a major component.

It is now more than 25 years since laboratories of biological analysis participated in the National Quality Control programme in Parasitology under the scientific responsibility of Dr. J.C. Petithory: this was optional until 1979, and obligatory thereafter. They receive twice a year a culture medium inoculated by the Mycology Unit of the Institut Pasteur of Paris. Laboratory personnel have to identify the fungus and send their results to the organizers of the control, the *Agence du Médicament*. After each exercise, participants receive an individual report with comments, followed soon after by an analysis of the participants' results together with a fact sheet in which an expert reports the characteristics of the fungus that has been, or should have been, identified.

The synthesis of the participants' results is published on the «Annales du Contrôle National de Qualité» distributed by the Unité de Biologie Médicale, Direction des Laboratoires et des Contrôles, Agence du Médicament, 143-147 Boulevard Anatole France, 93285 Saint Denis Cedex, France. Chief of the Unit is Dr. P. Maisonneuve.

At each mailing, three different specimens are distributed to the participating laboratories, randomly divided into three groups.

Since the beginning of the Quality Control programme, that provides twice a year distributions, French biologists have had to identify and become more familiar with more than 120 different fungi.

Over the years an improvement in performance has been observed, as shown in table 1.

Table 1

Species to be identified	% of correct results (year)	% of correct results (year)
Candida krusei	66% (1988)	77% (1994)
Epidermophyton floccosum	55% (1991)	63% (1994)
Fusarium oxysporum	55% (1989)	65% (1994)
Aspergillus niger	78% (1985)	92% (1997)
Torulopsis glabrata	82% (1993)	85% (1997)

From "Annales du Contrôle National de Qualité"

Even if the results are reasonably satisfactory, concerning the species to be identified, an improvement in the performance has been observed. Apart from rare cases, the performance continued to improve year by year. Thanks to the information sheets received, biologists have begun to have a greater knowledge of medical mycology and continued to be more interested in this important branch of the medical biology, previously neglected by most of them.

Analysis of the results reveals the reasons for mistakes, as depicted in the following tables (2-4).

Table 2 illustrates the different identifications reported for a strain of *Trichophyton soudanense*, an anthropophilic dermatophyte frequently isolated in France from patients of African origin. For this culture 1318 replies were received by the organiser in the allotted time.

Table 2

Identification	%
Trichophyton soudanense	36.2%
Microsporum audouinii	17.4%
Trichophyton mentagrophytes	10.0%
Trichophyton tonsurans	8.1%
Trichophyton rubrum	5.4%
Trichophyton schoenleinii	3.9%
Microsporum langeronii	2.4%
Trichophyton verrucosum	1.9%
Microsporum canis	1.9%
Trichophyton sp	1.5%
Other dermatophytes	1.3%
Yeasts	0.7%
Other filamentous fungi	0.3%
No replies received	9.0%

From "Annales du Contrôle National de Qualité", 12, February 1998

Table 3 shows data on a culture of *Aspergillus fumigatus* for which 1307 replies have been received within the specified date. Table 4 shows results with a culture of *Saccharomyces cerevisiae*, the worst score ever observed. Within the time limit, 1330 reports were submitted.

As it concerns mycology, the National Quality Control in France is

Table 3

Identification	%
Aspergillus fumigatus	59.5%
Aspergillus niger	32.7%
Aspergillus flavus	1.8%
Aspergillus nidulans	1.2%
Aspergillus sp.	0.4%
Mucoraceae	1.1%
Other fungi	0.2%
No replies received	3.1%

From "Annales du Contrôle National de Qualité", 12, February 1998

Table 4

Identification	%
Saccharomyces cerevisiae	33.5%
Saccharomyces sp.	12.3%
Candida parapsilosis	13.7%
Torulopsis sp. + *T. glabrata*	6.2%
Rhodotorula sp.	4.8%
Candida kefyr	4.5%
Candida krusei	4.1%
Candida tropicalis	2.8%
Cryptococcus sp. + *C. neoformans*	1.7%
Candida guilliermondii	1.4%
Candida albicans	1.2%
Other yeasts	1.8%
No replies received	12.5%

From "Annales du Contrôle National de Qualité", 12, February 1998

adapted to the participating laboratories, which are mostly multifunctional. Services offered include identification of fungal cultures and in certain cases serum samples for mycoserological examination.

The high number of participants does not make an extension to all other European countries feasible. The possibility exists, however, of organising controls adapted to the needs of specialised European laboratories.

The French National Quality Control, celebrating the 20th anniversary in 1999, has proved its importance in mycology as well as in other biomedical disciplines. It has helped to improve the knowledge of mycology and of quality control performances.

Alain Leblanc

The importance of Quality Contro has greatly increased during the past decades as a consequence of the increased number of deep-seated and superficial mycoses and the development of rapid diagnostic tools, in use in both specialized and non specialized laboratories. By now, the Quality Control is regarded as having an essential role as a means of permanent training. Some countries have had experience Quality Control in mycology for many years, whereas others have not yet started to organize a Quality Control programme. It is an ECMM purpose to make the European mycological societies aware of the importance of the systematic use of Quality Control and to encourage the exchange of different experiences.

Epidemiological Working Groups of ECMM

Epidemiological Survey on Cryptococcosis in Europe

Notes for participants

Last May, in Glasgow, the national coordinators of the Working Group on Cryptococcosis met to discuss the progress of the study.

Prof. Viviani informed the group that Dr. Dromer had resigned from the role of convenor of the study but would continue in the capacity of national coordinator for France. On Dr. Dromer's resignation the function of convenor was assumed by Prof. Viviani.

There was considerable country to country variation in the number of cases reported as shown:

Country	Total cases July '97-April '98	Cases for which strain is available
Belgium	11	4
Bulgaria	-	-
France	62	62
Germany-Switzerland	8	7
Greece	9	9
Israel	2	2
Italy	52	48
Poland	4	4
Portugal	5	5
Russia	2	1
Spain	3	2
Sweden	1	1
The Netherlands	4	0
Turkey	-	-
United Kingdom	28	28
Total	191*	173

* 75% associated with AIDS

Some countries had the advantage of a pre-existing national network for mycological surveillance or a mycology reference centre. Reasons for the difficulties encountered in other countries have been identified as objective obstacles or the isolated position of the coordinator which have hampered attempts at data collection despite their efforts and enthusiasm.

Some of the forms were incompletely filled-in and these cases will have to be excluded from the final analysis. The convenor emphasised that the study must be exhaustive at the national level and encouraged the coordinators to find ways to involve clinicians and mycologists in reporting cases. She advised coordinators to request that completed forms should be faxed to them as soon as possible as omitted information or mistakes could more easily be rectified if the patients documents were readily available.

It was stressed that obtaining the isolate from each case is mandatory to enhance the scientific value of the survey. Many of the basic objectives of this epidemiological study such as the determination of serotype, genotype and antifungal susceptibility profile will be reached only through the analysis of strains.

From analysis of the forms received it is apparent that in some cases differentiation between "unsuccessful treatment" and "relapse" is unclear. After discussion, the coordinators reached consensus on the following definitions:

Successful treatment: Resolution of clinical signs and symptoms, and sterilization of two sequential (one week apart) samples such as CSF and blood.

Relapse: Recurrence of infection, proved by isolation of *Cryptococcus neoformans* from clinical samples, at least six weeks after successful treatment. (NB Rising antigen titres alone are not necessarily indicative of active infection.)

The coordinators decided that information on two additional predisposing factors would be of value (a modified form is included in this issue):

1. In the case of AIDS patients whether

antiretroviral therapy had been given for more than two months before the diagnosis of cryptococcosis.
2. In the case of organ transplant recipients whether tacrolimus had been administered.

This additional information will help to determine whether there is a difference in the incidence and/or clinical presentation of cryptococcosis in AIDS patients who were given antiretroviral therapy before the diagnosis of fungal infection; and if there is a relationship between tacrolimus therapy and the development of cryptococcosis in organ transplant recipients as suggested in a report by Singh N. et al. CID 1997; 24:179.

To improve the diagnosis of cryptococcosis a document has been produced by Françoise Dromer in collaboration with Elizabeth Johnson. This is to be found on the reverse of the amended form enclosed in this issue.

Maria Anna Viviani

National coordinators of the Working Group on Cryptococcosis

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Epidemiological Survey on Histoplasmosis in Europe

Preliminary Report

Table 1: Distribution of reported cases of histoplasmosis between January 1995 and December 1997 according to country

Country	Proven	Suspected
Denmark	2	0
France	11	0
Germany, Austria and Switzerland	6	0
Turkey	1	0
UK	12	14

Table 2: Risk factors for reported cases of histoplasmosis between January 1995 and December 1997

Risk factor	No. of cases
None stated	4
AIDS	13
Trauma	1
Surgery	1
Malignancy	2
Caves	1
Steroids	1
Other	1*
Total	24

* From transplanted liver

A brief report of the ECMM Histoplasmosis survey was presented at the 4th Congress of the ECMM in Glasgow and this report summarises the data.

Twenty countries have been included in the survey, although two countries, Hungary and Russia, are still without national coordinators. Completed survey forms were received from France, the UK, and the Germany, Austria, Switzerland grouping; with limited information received from Denmark and Turkey.

Between January 1995 and December 1997, there were 32 cases of proven histoplasmosis, with 14 suspected cases. The distribution of cases by country is shown in Table 1.

The risk factors for the reported cases are shown in Table 2.

Only 2 cases of histoplasmosis have been reported for 1998.

It was decided to modify the survey form slightly to include information on the histological diagnosis of the disease and also to clarify certain questions. The amended form is available from your national coordinator.

Although the isolates of *Histoplasma* are not being kept from the survey, any sera or histology from patients would be of interest and should be sent to your national coordinators.

Many thanks to those people who have provided information so far and please continue to collect information to ensure that the survey is as accurate as possible. Further information, suggestions or ideas should be sent to Dr. R. Ashbee or Prof. E.G.V. Evans
(Fax +44 113 233 5640;
E-mail: <h.r.ashbee@leeds.ac.uk> or
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Ruth Ashbee and E.Glyn V. Evans

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Epidemiological Survey of Nocardiosis and other Aerobic Actinomycetes Infections in Europe

Preliminary Report

The "Epidemiological survey on nocardiosis and other aerobic actinomycetes infections in Europe" would permit to collect enough data on these scarce infections and to realize more sophisticated analyses. This needs to likely strenghten national reporting systems, to establish a common case definition and a minimum set of diagnosis tests. This survey began in July 1997 and should last at least two years. All nineteen ECMM delegates were contacted and asked to appoint a national coordinator. Sixteen were identified (Italy, Switzerland, Bulgaria, Czech Republic, Germany, Greece, Hungary, Poland, Portugal, Russia, Spain, Sweden, The Netherlands, Turkey, United Kingdom, France).

In Switzerland, 13 of 24 medical centers contacted accepted to participate to the study. At this date, 8 cases were identified (2 *Nocardia asteroides*, 1 *N. farcinica*, 1 *N. brasiliensis*, 1 *Streptomyces* sp., and other upon identification). In Italy, 52 of 241 centers contacted accepted to participate, permitting to collect at this date 21 strains, including one isolate of *Actinomadura madurae*. Russia informed of a total number of 16 cases without sending strains. Czech Republic indicated that none actinomycete infection was diagnosed, and Poland reported that actinomycete infection cases seem rare. Turkey informed of 3 cases without sending any strain. Germany should send aggregate data in near future. In France, 265 correspondents were contacted in 1997. Ninety-four aerobic actinomycete strains were identified, including 66 *Nocardia* spp. No figure was yet obtained from other countries.

Identification of aerobic actinomycetes isolated in France revealed 28 isolates of *N. asteroides*, 19 of *N. nova*, 7 of *N. farcinica*, 10 of *N. brasiliensis*, 2 of *N. otitidiscaviarum* (so 66 isolates of *Nocardia*) and 28 isolates of other aerobic actinomycetes (*Streptomyces* sp. for 23 isolates). From the preliminary data for nocardiosis, we could underline:

- the mean age was 54-year-old but 48% at

56 to 75-year-old,
- for 33%, nocardiosis was diagnosed in apparently immunocompetent patients,
- lungs were the major location of the infection, especially by *N. asteroides* and *N. nova*,
- the first cause of immunodepression was a corticotherapy (21 of 32 cases),
- *N. brasiliensis* was isolated from one pulmonary and two extra-pulmonary infections in immunocompromised patients,
- three cases of disseminated infections occurred only in immunocompromised patients,
- *Nocardia* spp. and especially *N. farcinica* strains are naturally resistant to many antibiotics.

The in vitro most active agents were:
- for *N. asteroides*: amikacin (100% of all strains tested were susceptible), imipenem (97%), cephalosporins of third generation (93%), and minocycline (86%),
- for *N. farcinica*: amikacin (100%), amoxicillin-clavulanic acid (100%), minocycline (100%), and imipenem (88%),
- for *N. nova*: imipenem (100%), amikacin (100%), cefotaxime (85%), erythromycin (95%), minocycline (85%), and ampicillin (80%).

These preliminary data on nocardiosis are interesting, encourage to continue the survey, prove that an European survey is not an utopia, but emphasize the need of further standardisation of the data collected.

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Epidemiological Survey on Candidemia in Europe

Notes for participants

The national coordinators of the Candidemia Working Group met last May in Glasgow. The convenor re-stated the aims of the epidemiological study "Candidemia in Europe": 1. to emphasize the progress and evolution of candidemia among the various categories of patients, 2. to underline that this fungal infection and its related complications are still underestimated by practitioners in many countries or institutions and to stress the major economic burden for patients and society of invasive *Candida* infections.

Objectives of the study differed from those of the other ECMM Groups. The "Epidemiological Study of Candidemia" does not intend to be exhaustive at the country level, but to be exhaustive at the level of each participating hospital. Trying to identify all the candidemia cases occuring in a country would not be realistic. On the other hand, a study correctly designed at the level of some hospitals or institutions in the European countries would make health practitioners more sensitive to the severe prognosis of candidemia and would give a more documented basis of the present situation.

In certain hospitals or countries, development of the survey is hampered by problems such as: 1. low motivation of physicians for the survey (no candidemia in their ward!...), 2. lack of money for biological diagnosis (automated blood culture systems, vials and kits for identification) considered as too expensive, 3. small automated systems settled directly in the wards. So vials positive for yeasts are not always sent to the labs for the species identification, or patients receive empiric treatment if a candidemia is suspected.

The convenor recommended:
- identification of the institutions where efficient collaboration of an experienced mycologist is available,
- notification of all candidemia cases diagnosed during the two year study period, filling in the forms and storing the strains,
- some general information should be got for each participating hospital (concerning mainly the number of admitted patients for a duration higher than one day during the period of the survey).

As regards the forms, filling the candidemia forms is the main source of the difficulties met in the study. Thus simplification of forms is strongly recommended by some coordinators, clinicians being sometimes discouraged by the amount of data to document.

It is the opinion of the convenor that a high level of documentation of the candidemia cases is a basic condition for publishing the results in a peer reviewed journal. Consequently, national coordinators have an important role in supervision and helping to stimulate participation; they have also to encourage microbiologists of the participating centers to go themselves to the units and to gather information if possible the same day that yeasts were detected in the blood culture.

As regards the strains, obtaining them is mandatory in the study: these will be protected according the rules defined for the "ECMM Epidemiological Working Groups". Strains must be stored by the national coordinators and sent to the convenor at the end of the two years study period.

Defining potential satellite studies is too early yet: obviously, these studies could be an excellent reason to encourage participation in the survey. Susceptibility testing or molecular investigation of a great number of *Candida* strains isolated from well-documented septicemia cases would be of high scientific interest.

Giving a full synthesis of the results obtained so far at the European level only some months after the start of the study is evidently not possible. However some very preliminary comments can be made from the documentation of 350 cases of candidemia (occuring in 8 countries - Greece, France, Hungary, Israel, Italy, Spain, UK - between September 1997 and

March 1998) in about one hundred institutions. These first comments were presented at the Glasgow Conference.

- Firstly, concerning the spectrum of yeast species isolated from blood, two clearly surpass the others: *C. albicans* (55% of isolates) and *C.* (*Torulopsis*) *glabrata* (20%) which is becoming the second pathogen in candidemia. An important difference has been observed according to the countries about the frequence of *C. krusei* septicemia (0 to 20% of isolates).
- Antifungal therapy of candidemia is based mainly on administration of amphotericin B IV (30 to 70%), but fluconazole is more and more employed (18 to 53%). However candidemias are systematically treated in only one country out of six (according to the first report from five countries, 12 to 25% of the candidemia cases were not treated).
- Fatality rate of these infections appears very high since 25 to 50% of patients died within the 30 days following the yeast detection in blood. Comparison between two countries (more than one hundred of candidemia cases diagnosed in each one) shows that the fatality rate can significantly vary according to the species responsible: in the first one, infection is fatal in 80% of candidemias due to *C. krusei* (60% for *C. albicans*, 40% for *C. tropicalis*) and in the second country, mortality due to *C. tropicalis* (62%) is the highest (50% and 30% mortality for candidemia due to *C. albicans* and *C. glabrata*, respectively).
- Finally, incidence rates of candidemia (4 countries, 76 hospitals) seem to be between 0.1 to 4.3 /10,000 patients hospitalized (>one day).

We stress again that these figures are still very preliminary and the observations mentioned above must be interpreted cautiously. However they confirm the interest in such a study to acquire more information on the epidemiology of candidemia in Europe and to promote collaboration between mycologists at national and European levels. This kind of survey will certainly need a lot of effort and work from everyone, but we are convinced of the ultimate success and benefit of our future involvement.

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Epidemiological Survey on Tinea Capitis in Europe

Interim report

Participants in this study were asked to provide figures on the numbers and identity of isolates from cases of tinea capitis received by their departments in the year 1997; in addition where possible they also gave similar data for the year 1987. They were asked to provide some information on the source of material ie urban, rural or mixed populations and whether it was diagnostic or reference (or both). As of July 10th 1998 returns have been received from 98 laboratories in 14 countries through Europe. Ninety seven of these produced figures for the year 1997 but 50 had similar figures for 1987.

The numbers reported by the laboratories are shown in the enclosed table. For each year the figures for all laboratories are compared with those receiving culture material from predominantly urban sources.

These results show two trends a) an overall increase in the numbers of cases of anthropophilic isolates between 1987 to 1997 b) this changed pattern is mainly due to results from laboratories receiving scalp material from cities.

43 out of 87 laboratories reported an increase in anthropophilic cases and this was associated with patients of African or Caribbean origin in 26 out of 32 responses.

Overall the pattern of anthropophilic infection varies somewhat within Europe where over 70% of isolates of *Trichophyton tonsurans* were seen in the United Kingdom and over 55% of isolates of *T. soudanense* and *Microsporum audouinii* or *M. langeroni* were seen in France.

In fact most laboratories reported cases of *M. canis* (86%), whereas the percentage of laboratories reporting cases of *M. audouinii*, *T. tonsurans*, *T. soudanense* and *T. violaceum* were 32, 46, 57 and 28% respectively. This suggests that the distribution of *M. canis* cases is wider although numbers are fewer - an observation which is in keeping with a sporadically occurring infection.

	1997		1987	
	All	Urban	All	Urban
M. canis	1432	259	1097	370
*M. audouinii**	409	309	168	159
M. rivalieri	38	5	14	2
Microsporum spp	17	8	2	2
T. tonsurans	873	692	54	12
T. violaceum	364	286	198	163
T. soudanense	392	362	210	209
T. gourvilii	5	5	4	0
T. schoenleinii	3	1	11	4
T. verrucosum	30	8	16	1
T. mentagrophytes	209	20	182	17
T. rubrum	8	7	12	3

* Includes *M. langeroni*.

Only 13 laboratories reported that childrens' scalps were regularly inspected at school and in 8 answers inspections were designed to detect pediculosis capitis rather than tinea capitis. The main treatment used is still griseofulvin in 55 out of 65 of those reporting drug usage.

A few more results are awaited but the data are interesting and suggest that there is a significant increase in anthropophilic infections in Europe particularly in cities and that these vary from country to country. Many such cases are associated with children of African or Caribbean ancestry. By contrast the countries with the highest numbers of cases of *M. canis* are those in southern Europe - Greece, Italy and Spain. It is proposed that members of the group work further to identify the means of preventing further spread of anthropophilic infection in cities within Europe.

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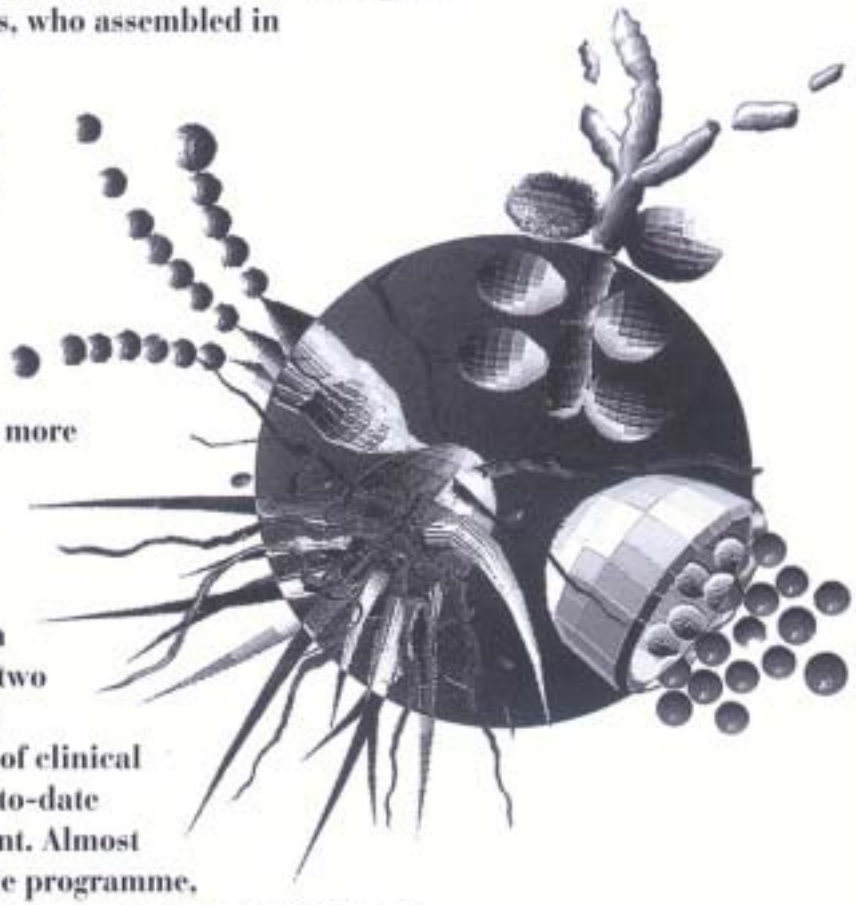
Special report on...

by
Donald W.R. Mackenzie

Focus on Fungal Infections 8

The previous issue of the Mycology Newsletter contained a report on Trends in Invasive Fungal Infections 4. The precedent and to some extent the model for this successful series were the annual Focus on Fungal Infections meetings held in the United States. The most recent of these was held in Florida in March (1998). Like earlier meetings, it attracted several hundred participants, who assembled in Florida to hear a panel of experts summarise current knowledge on the mycoses, with particular reference to recent developments in epidemiology, clinical and laboratory aspects, and antifungal therapy.



The intention of these meetings is to provide up to the minute information on all major aspects of clinical mycology. Focus meetings are more informal and more structured than conventional conferences. All speakers are invited. Material presented can be very recent. Thus, some of the information had first been presented at a major conference only two weeks previously. The Focus meetings attract a comparatively large number of clinical and laboratory personnel seeking up-to-date information and authoritative comment. Almost 40 eminent speakers contributed to the programme, which included overview lectures, podium and poster sessions, and special sessions where controversial topics were debated by supporters of opposing views. The two-day meeting was preceded by an optional workshop on culture and identification of selected medically significant fungi.

This was the 8th of the series. It was held in Orlando (Florida) between 4th-6th March, 1998. The topics included Mycoses and HIV

chaired by
William G. Powderly

Session I

Mycoses and HIV infections - the big change?

infections-the big change?: Recent developments in selected mycoses: Superficial and cutaneous mycoses: Opportunistic mycoses: Current happenings in antifungal therapy: Antifungal resistance - the continuing saga: Therapeutic pot-pourri: Laboratory-clinical correlations.

After an address of welcome by Elias J. Anaissie (Little Rock, Arkansas), Glenn D. Roberts (Rochester, Minnesota) opened the first session with an introductory lecture on «The ever expanding significance of mycoses in human medicine». The changes in orientation of mycology in the past 25 years were reviewed, the main impact being caused by the marked shift towards immunocompromised patient populations, and the attendant increase in opportunistic infections. There has been a significant trend towards declining financial support, with fewer trained personnel. Electronic transfer and availability of information through direct access to data bases and the Internet are proving valuable for education, training, and diagnosis. New digital processes have made it possible to store data, including digital images, which can lead to improved interactive consultation between clinical and laboratory personnel.

The conference programme was divided into eight separate topics. The first (Mycoses and HIV infections - the big change?) focused on changes within the AIDS era, and was introduced by Peter G. Pappas (Birmingham, Alabama), who presented a «Review of mycotic infections in HIV disease between 1980-1995». During this 15 year period, mucosal candidosis was the commonest fungal infection: *Candida* oesophagitis was recognised as an AIDS defining condition. Treatment of fungal opportunistic infections with ketoconazole later gave way to fluconazole, but with increased use treatment failure was recorded in patients with oropharyngeal candidosis. Fluconazole resistance was also observed in vitro. As the era progressed, fluconazole was used prophylactically in patients with CD4 counts of 100 or less. Early results with itraconazole were promising.

Cryptococcal infections increased during the AIDS epidemic, and also became an AIDS defining illness. Meningeal forms occurred in about 85% of cases, the incidence in AIDS patients varying from 7-30% in different countries. Combination amphotericin B and flucytosine was the original standard therapy, but relapses were common. Studies have shown that fluconazole produced better suppression than amphotericin B, but that deaths tended to be earlier. By 1995, the standard approach was to use amphotericin B for 2 weeks, followed by fluconazole. Other systemic opportunistic mycoses in AIDS patients included histoplasmosis and coccidioidomycosis. Prevalence in endemic areas could be high. Prior to 1990, treatment of choice was amphotericin B or ketoconazole, but this later gave way to itraconazole. Fluconazole has proved useful in the treatment of coccidioidal infections of the central nervous system.

Fluconazole and itraconazole have had a major impact, although the development of resistance to fluconazole remains a cloud on the horizon.

Robert A. Larsen (Los Angeles, California) then reviewed the changes since 1995, the year that protease inhibitors were first introduced. This, in combination with the widespread use of intermittent fluconazole prophylaxis has led to a sustained decrease in serious fungal infections. The reduction in incidence of cryptococcal and *Candida* infections has been in the neighbourhood of 70%. The relationship between CD4 counts and opportunistic infections in general were considered in relation to mono- or triple therapy. Data were presented to show that suppression of HIV replication is very important in preventing opportunistic infections. When the viral load was <35,000 copies, the risk of opportunistic infections was 10%, rising to 40% when >35,000 but <200,000, and 70% if RNAse copies were not reduced. In patients not receiving triple therapy, opportunistic infections occurred within 4 months, but in treated patients, this fell to 2 months.

Experience based on clinical experience at University of Southern California, Los Angeles, suggest that intermittent prophylaxis with fluconazole is as effective as daily doses for both *Candida* and cryptococcal infections, and that fluconazole is superior to itraconazole in preventing relapse of cryptococcal meningitis.

Two additional presentations provided alternative views on the magnitude of the problem posed by opportunistic fungal infections. In the first, Charles P. Farthing (Los Angeles, California) emphasized the reduction in numbers of opportunistic fungal infections following the introduction of triple therapy. In one published study, only 54% of patients were in control of their HIV, but other studies show that 80% of patients have significant reductions in HIV, sometimes to the point of undetectibility.

Thomas Patterson (San Antonio, Texas) took a different view, suggesting that the reduction in numbers of mycoses was more apparent than real. Numbers of fungal species implicated as agents of OI is constantly increasing. There has been a reduction in numbers of mycoses, but they are still a significant clinical problem. Moreover, the development of fluconazole resistance is a potential problem in the management of these patients.

In recent years, it has often been reported that infections caused by species of *Candida* other than *C. albicans* have been on the increase. This topic was considered by Mary H. White (New York, New York). Although well documented, experience at the Memorial Hospital, Sloan Kettering Institute suggests that in some instances the increases may be apparent rather than real. There appears to be a marked difference in hospital specificity, prevalence of non-*albicans* varying markedly from centre to centre. It was found that an apparent decline in numbers of non-*albicans* isolates at the Sloan Kettering Institute preceded the introduction of fluconazole. A number of possible explanations for the variation in numbers of non-*albicans* isolated were advanced, including improved catheter practice, changes in laboratory practice (for example not speciating *Candida* isolates), and alteration in the selection criteria of patients and procedures for blood cultures and total parenteral alimentation. Any change in the aetiological spectrum of candidosis is likely to be multi-factorial, of which fluconazole is only one.

chaired by
Stephen E. Sanche

Session II

Recent developments in selected mycoses

The second session focused on «Recent developments in selected mycoses». Thomas J. Walsh (Bethesda, Maryland) spoke on «Newer methods of diagnosis for invasive candidiasis and aspergillosis - are there any that really work?». A wide range of methods were reviewed. Established diagnostic aids include antigen tests for cryptococcosis and histoplasmosis, and antibody tests for coccidioidomycosis.

Methods for diagnosing invasive candidiasis include patient evaluation, diagnostic imaging, blood cultures, and biopsy. In recent years, advances have been made in blood culture technology. However, not all patients with autopsy-proven invasive candidiasis have demonstrable candidaemia. It was shown in autopsy studies that when *Candida* infection was present in 3 or more sites, blood cultures were positive in about 80% of cases. When fewer than 3 sites were infected, the proportion of positive blood cultures was markedly reduced. Candidaemia is therefore probably not the single defining finding for invasive candidiasis; additional supportive test procedures are required.

More recent advances in antigen purification, monoclonal antibody production, epitope mapping, recombinant DNA techniques and PCR technology have provided new possibilities for detection of invasive fungal infections. Among the *Candida* products and test systems are mannans (detected by EIA or latex), beta-glucans (Tachypleus assay), d-arabinitol (rapid enzymatic assay and mass spectroscopy), and cytoplasmic antigens including enolase and the breakdown product of the HSP90 *Candida* heat shock protein (EIA). PCR methods, not generally available at present, have reached high levels of sensitivity and specificity (70-100%), but their sensitivity for blood culture negative deep seated candidiasis remains low. Although each of these markers and systems have proven utility in clinical trials, a range of factors have limited their introduction into clinical practice.

The importance of multiple sampling for any test procedure was emphasized. Thus, the test for enolase was positive in 54% of 24 cases of proven invasive candidiasis when a single sample was tested, rising to 75% when additional sera were tested. Tests for antigenaemia can be positive in the absence of candidaemia. Results with collaborative trials based on detection of d-arabinitol showed that 62% of cases of invasive candidiasis were detected.

In the detection of invasive aspergillosis, radiographic images are

of value. Biopsy and culture results can be definitive, as can direct examination and culture of bronchalveolar fluid. Because many patients have haemostatic defects which preclude invasive diagnostic procedures, alternative approaches have been made, including detection of galactomannan antigenaemia by radioimmunoassay or EIA. A commercially available latex agglutination test is specific but of lower sensitivity than a double sandwich enzyme immunoassay. Results with PCR are encouraging when applied to analysis bronchalveolar fluid or serum, and may prove to be a valuable diagnostic aid.

A new PCR system, using universal primers and specific probes may also prove useful in diagnosing infections caused by less common pathogens, such as species of *Fusarium*, *Trichosporon*, zygomycetes, and dematiaceous moulds.

It was emphasized that most non-culture detection systems are intended to complement rather than replace conventional diagnostic approaches. Reliance cannot be placed on any single test procedure. For establishing a diagnosis of invasive candidiasis or aspergillosis or monitoring therapeutic responses, data derived from a panel of diagnostic systems should be used.

Michael G. Rinaldi (San Antonio, Texas) reviewed infections caused by pigmented fungi («Phaeohyphomycosis: what's colorful with the dark fungi?»). The range of causal agents is wide, and includes both yeasts and moulds. Most are filamentous fungi lacking a sexual form *(Hyphomycetes)*. Some of the associated diseases have been superficial; others are deep-seated. Presentations are sometimes bizarre. They have been found in both "normal" and immunologically altered subjects. Diagnostic laboratory procedures were reviewed in relation to individual case histories. These included aetiology, histopathology, diagnosis and therapy.

David S. Bauman (Washington, Oklahoma) gave a comprehensive review of current serodiagnostic procedures («Serodiagnosis of mycotic infections; what works and what does not»). Some 25 tests were considered, developed as diagnostic aids for infections caused by species of *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma* and *Sporothrix*.

Session III

chaired by
Sanjay G. Revankar

Superficial and cutaneous mycoses

The third session focused on «Superficial and cutaneous mycoses». Roderick J. Hay (London, United Kingdom) presented a keynote address on the «Diagnosis and treatment of superficial and cutaneous mycoses». After showing clinical features of infections with species of *Alternaria*, *Saccharomyces* and *Fusarium*, attention was paid to two current problems in clinical practice, viz. nail and scalp infections.

About 85% of cases of onychomycosis are caused by dermatophytes. The range of causal agents is wide. Different surveys have shown prevalence rates of 2-18%: Terbinafine, administered orally, provides a cure rate of about 82%, compared with ca. 20% for griseofulvin. Pulse therapy with itraconazole is based on the strong binding affinity that exists between the drug and keratin, single pulses consisting of 400 mg daily for a week. Fluconazole is also effective.

Some 20% of patients fail to respond to treatment. A possible explanation includes the occurrence in dystrophic nails of localised areas of disorganised keratin, which are unaffected by treatment with azoles, but within which viable fungal elements are present.

Attention was drawn to causal agents such as *Scytalidium hyalinum*, *Scopulariopsis brevicaulis* and *Aspergillus* spp.

Candida onychomycosis presents special problems. Elimination of the yeast may not rectify the clinical abnormality. Infections with species other than *C. albicans* are less likely to respond to treatment.

Problems in dealing with onychomycosis include ascribing significance to the isolation of moulds from dystrophic nails, and the current emphasis in clinical practice on keeping costs low.

Recent attention on scalp ringworm focused on the eradication campaigns in the 1960s, supported by the WHO, and on the northward spread of *Trichophyton tonsurans* into the United States. Problems in the management of tinea capitis include differing aetiologies and natural histories of the infecting agents, and the occurrence of carriers. Diagnosis on the basis of clinical features alone can be relatively effective, but only when assessments are made by experienced personnel. Figures on the prevalence of tinea capitis in the community are imprecise, low levels being linked to lack of awareness.

Boni E. Elewski (South Euclid, Ohio) described the clinicians approach to treatment of skin infections, by referring to patients with tinea capitis, pityriasis versicolor and onychomycosis.

Michael T. Walsh (Orlando, Florida) reviewed the procedures involved in diagnosis of fungal infections in animals, emphasising the basic similarities in approach to the management of human mycoses.

Session IV

chaired by
John W. Hiemenz

Opportunistic mycoses

The 4th session dealt with «Opportunistic mycoses», and was introduced by Nina Singh (Pittsburgh, Pennsylvania), who spoke on «Fungal infections in solid organ transplant recipients». Most infections are caused by Candida or Aspergillus, although cryptococcosis, phaeohyphomycosis, zygomycosis and endemic geographically restricted mycoses can also occur. The incidence of invasive aspergillosis varies from <1% in renal transplant patients to 8.5% in lung transplants. Mortality in the latter group is about 75%, but slightly lower with ulcerated tracheobronchitis, a unique form of aspergillosis found in lung transplant patients. Risk factors vary according to the type of transplant. These include cytomegalovirus, single lung transplantation, structure and functional status of the lung, intensity of immunosuppression, and renal failure. Colonization with A. fumigatus is not necessarily a contraindication to lung transplantation.

In one series of 2,500 liver transplants, 26 cases of invasive aspergillosis were recorded, about 25% occurring in re-transplant patients. In such cases, the disease occurs early, often while the patient is still in intensive care after the transplant. Immediately after transplant, the new allograft begins to sequester platelets, so most post-transplant patients are thrombocytopenic. Brain abscesses are a significant consequence of transplantation. In one series, virtually all abscesses were caused by fungi. In one analysis of 5,000 solid organ transplants, 94% of brain abscesses in liver transplants and all of the renal transplants were fungal.

Candida infections account for about 30-90% of all fungal infections. The most common sites of infection are mediastinal or pulmonary infections in heart or lung transplant recipients, and wound infection in pancreatic and intra-abdominal infections in liver transplant recipients. Significant risk factors include serum creatinine levels, re-transplantation, and colonization of 3 or more sites.

Elias J. Anassie (Little Rock, Arkansas) then spoke on «Invasive aspergillosis: a new look at an old disease». The widespread use of prophylactic fluconazole in cancer patients has reduced the incidence of deep-seated candidiasis, but left invasive aspergillosis as an important cause of disease. It presents in a variety of ways. Diagnosis is achieved by a combination of clinical and laboratory findings. Culture of bronchalveolar lavage fluid has not proved very successful in establishing a diagnosis of invasive aspergillosis, being positive in only 1 of 11 patients. The appearance of CT scans is helpful, as is the new Pastorex test for detection of antigenaemia, particularly in terms of negative predictive value. PCR methods are both sensitive and specific, but too expensive for routine use.

Treatment can be difficult. Amphotericin B remains the drug of choice, although itraconazole has a role in the follow up treatment of patients who have recovered from neutropenia and are ready for treatment as outpatients. Lipid formulations of amphotericin B should probably be confined to patients with deteriorating renal function.

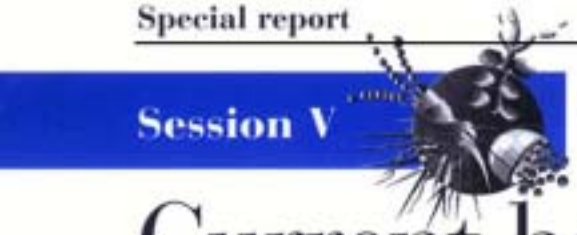
Several studies have shown the presence of *A. fumigatus* in the hospital environment, being recoverable room HEPA filters and water supplies. In view of the continuing importance of invasive aspergillosis, attention to the environmental origin of infections is warranted.

The session concluded with a special keynote address by William R. Jarvis (Atlanta, Georgia) on «Nosocomial mycotic infections: emerging pathogens with new lessons». About 75% of such infections are caused by *Candida* spp. Those caused by *Aspergillus* spp. are much less common (<2%). The occurrence of infections by less common pathogens was illustrated by reference to individual outbreaks. Endophthalmitis, caused by *Acremonium kiliense* was diagnosed in four patients following cataract operations. Environmental studies showed that the agent was present in a humidifier, which was downstream of a HEPA filter.

In another instance, *Candida* endocarditis was diagnosed in a patient receiving an aortic valve replacement. Investigations revealed that the allograft was culture positive when obtained from the donor. After antifungal treatment, the graft was culture negative, but genotyping showed that the isolates from graft and patient were identical. The patient improved following removal of the graft and administration of antifungal treatment.

A third outbreak involved a cluster of 15 infants in a neonatal intensive care unit, who became infected with *Malassezia pachydermatis*.

A point prevalence study identified a health care worker and 12 health care worker dogs to be harbouring the yeast. All but 3 of the isolates from dogs had identical patterns by restriction fragment length polymorphism studies. In a fourth example of nosocomial infection, *Candida* endophthalmitis affecting four patients was traced to an intravenously administered anaesthetic, two different genotypes of *C. albicans* being isolated from syringes containing the anaesthetic.



Session V

chaired by
William E. Dismukes

Current happenings in antifungal therapy

The morning of the second day began with the 5th session, which was devoted to «Current happenings in antifungal therapy». The first contribution was by Frank C. Odds (Beerse, Belgium) who spoke on «Prospective correlation of in vitro susceptibility data with patient outcomes». It is well known that in the laboratory, the outcome of a test result is influenced by many factors. Carefully constructed and conducted cooperative studies organized by the NCCLS Antifungal Subcommittee has led to the establishment of a reference method. By its means, break points have been determined for fluconazole (64 µg/ml) and itraconazole (1 µg/ml). The principal consideration is whether or not a correlation exists between MIC values and clinical outcome. In practice, if a physician learned that a clinical isolate was resistant to an antifungal drug, treatment with that drug would probably be withheld.

Studies have been conducted by the NCCLS subcommittee on clinical outcome in relation to susceptibility. Of 403 patients infected with isolates sensitive to fluconazole, 92% responded clinically. The comparable response rate in 61 patients from whom resistant isolates were obtained was 56%. Results with itraconazole were similar. If the question asked is "Can MIC results predict treatment failure?" the answer must be "no!". Data from other published studies have sometimes been contradictory, but the numbers of patients involved have generally been small. Even in those studies, however, it was found that patients infected with resistant isolates can respond to treatment.

MIC tests do not by themselves predict the outcome of therapy. Complicating factors in assessing the importance of laboratory testing include those relating to the drug, the host, and the infecting fungus. As to why patients infected with resistant strains may nevertheless respond to treatment, factors that could influence evaluation of responses to treatment include improvements in the patient's condition unrelated to therapy, and alteration in the behaviour of a fungal pathogen in vivo, rendering it incapable of functioning as a pathogen.

In the future, the focus of attention on minimal fungicidal levels or ratios of peak plasma levels to MICs may prove to be of value in predicting the outcome of infection. At present, however, results obtained by antifungal sensitivity testing can be regarded only as advisory.

Lisa Saiman (New York, New York) then spoke on «Treatment of neonatal candidiasis». Attention focused initially on the features of pre-term babies as they relate to candidiasis. Their unique features include relative immunodeficiency, reduced chemotaxis of neutrophils, low levels of immunoglobulins, and immature skin structure and gastrointestinal tract. Congenital neonatal candidiasis is rare; a more common forms of the disease is catheter-associated, usually secondary to endogenous fungal colonization of the gastrointestinal tract. Candidaemia is comparatively rare, being recorded in one prospective study on only 35 occasions.

Concerning the origin of infection, this can be endogenous, common source outbreaks, or person-to-person spread. Colonization rates are higher in neonates than in full term babies. Between 28-47% of very low weight babies are colonized, the commonest site being the gastrointestinal tract. Colonization of the respiratory tract is highly associated with invasive disease. Common source outbreaks have been associated with hyperalimentation, glycerine suppositories and intravascular devices. Spread via health workers' hands are well documented.

Conventional amphotericin B is the treatment of choice. Neonates have reduced localized and systemic toxicity and tolerate the drug well. Treatment may therefore be started at 1mg/kg/day without earlier loading doses. Lipid-associated formulations are being used although information on its benefits compared with conventional amphotericin B are lacking. Fluconazole is being evaluated as an alternative therapy to amphotericin B, but to date, there have been no trials comparing the two drugs in the management of candidiasis in preterm babies. It offers benefits in treating infants intolerant of amphotericin B, or infected with resistant species, such as *C. lusitaniae* or *C. glabrata*. Recommended dosage for premature infants is 6 mg/kg/day administered every 3 days for the first week, and every second days for the subsequent three weeks. Prophylaxis may have a role for very high risk babies.

Consideration was then given in the form of a dialogue on «Point-counterpoint on lipid-associated polyenes: the ID consultant (Donald A. Armstrong: New York, New York) to the transplant service chairman of the pharmacy & therapeutics committee (John H. Rex: Houston, Texas)». Donald Armstrong reviewed experiences to date with lipid formulations of amphotericin B. In retrospective studies, ABLC at 5mg/kg/d and conventional amphotericin B at 0.6-1 mg/kg/d had similar success rates (65% and 61% respectively) in the treatment of nosocomial candidiasis. In a prospective study sponsored by the Mycoses Study Group, involving almost 800 high risk neutropenic patients, AmBisome (3 mg/kg/d) and amphotericin B (0.6 mg/kg/d) also

had similar success rates (50% and 49%). Studies have shown that lipid formulations are generally less toxic and more effective than conventional amphotericin B.

John H. Rex conceded that such drugs were effective, but their high cost posed serious difficulties. Data were presented showing comparative costs (Table).

The high cost of these agents suggests that prior approval will be required, and that they will have to be balanced against the costs associated with treatment of drug-induced nephrotoxicity. Protocol guidelines for their use should be developed.

Drug	Usual dose	Acquisition cost	Cost/day (70-80 kg adult)
Conventional amphotericin B	0.7 mg/kg/day	$20/50mg	$20
ABLC (Abelcet®)	5 mg/kg/day	$80/100 mg	$320
ABCD (Amphotec®, Amphocil®)	3-6 mg/kg/day	$80/100 mg	$240-$400
Ambisome®	3 mg/kg/day	$157/50 mg	$785

This session was concluded by Richard W. Yee (Houston, Texas), who delivered a «Special lecture on diagnosis and therapy of fungal keratitis». The topics included pathogenesis, clinical manifestations, histopathology, diagnosis, and treatment with antifungals or surgery. Most current forms of treatment inhibit growth of the infecting agent and depend on the host for its eradication. Regular debridement of the base of a corneal ulcer is useful for elimination of the agent, necrotic stroma and other inflammatory debris. A conjunctival flap can still be useful in unresponsive cases.

chaired by
M. Hong Nguyen

Session VI

Antifungal resistance - the continuing saga

The 6th session was in the form of another dialogue, this time an informal debate between a husband and wife team, viz. Thomas F. and Jan E. Patterson (both of San Antonio, Texas) on «Antifungal resistance - the continuing saga».

Thomas Patterson expressed the view that although some resistance to azole antifungals has been reported, it is uncommon, and has occurred mainly in the context of oropharyngeal candidiasis in AIDS patients. Therapeutic responses can occur in patients infected with resistant strains, when treatment is maintained. The importance of host factors in determining outcome of infection was emphasized. It was suggested that although fungal resistance occurred, it was manageable, and did not constitute a major problem.

Jan E. Patterson demurred, pointing out that infections caused by resistant non-*albicans* species (such as *C. glabrata*, *C. lusitaniae*, *C. tropicalis*, *C. dubliniensis* and *C. krusei*) are increasingly common. Azoles are being used increasingly because of the toxicity of amphotericin B, and the high cost of lipid formulations. The spectrum of invasive fungal infections in nosocomial settings continues to increase, and simultaneously the importance of clinical resistance.

Both speakers agreed that injudicious use of antifungals should be avoided, and that resistance to antifungals has become an established clinical problem.

chaired by
John F. Toney

Session VII

Therapeutic potpourri

Session 7 was labelled «Therapeutic potpourri». The first speaker was John R. Graybill (San Antonio, Texas), whose topic was «The status of other antifungals: cell-wall active agents and drugs developed for specific molecular targets». Brief reference was made to the echinocandin drugs, but the major focus of interest was on two classes of antifungals entering clinical trials, both of which target the fungal cell wall. The first inhibits β 1-3 glucan synthase. Most of the available data on efficacy are based on experimental infections. Merck MK991 has been shown to be effective against systemic infections with *Candida* spp. at much lower doses than conventional amphotericin B. Good responses have also been observed in experimental aspergillosis and histoplasmosis. In one prospective study conducted in South America, the efficacy of the Merck product was evaluated in 128 patients with endoscopically proven *Candida* oesophagitis. Tolerance was good, and results were comparable to ampho-

tericin B. The drug has to be given parenterally.

The second class described are the Nikkomycins, which target chitin synthase. These were initially thought to be more effective against dimorphic pathogens such as *Coccidioides immitis* and *Blastomyces dermatitidis*, but they are also active against *Cryptococcus*, *C. albicans* and *A. fumigatus*. MIC values appear to be of limited value in predicting outcome of infection. Combination therapy with Nikkomycins and azoles may prove to be useful.

Many other potential antifungal targets have been identified, including topoisomerases and elongation factors.

John R. Wingard (Gainesville, Florida) then spoke on «The oncologic approach: combinations of antifungals and antifungals plus immunomodulators». Major factors in determining the outcome of fungal infections in oncologic patients are neutropenia and integrity of the mucosal barriers. The haematopoietic growth factors G-CSF and GM-CSF have been evaluated for prophylaxis in high risk patients, as adjuncts to antifungal agents, for the generation of "enhanced" granulocyte transfusions in normal donors, and for restoration of the mucosal barrier.

Both growth factors are highly effective in reducing the duration of neutropenia in the non-transplant setting, and in reducing the risk of infection. In one group of elderly patients with acute leukaemia given GM-CSF after chemotherapy, there was a marked reduction in numbers of fatal fungal infections, and a lower mortality rate. The lowered risk of infection was not seen in bone marrow patients, although the numbers reported to date have been relatively small.

The widespread use of growth factors and increasing use of blood as a source of stem cells has resulted in a shift in the occurrence of fungal infections from the neutropenia prior to engraftment to 2-4 months after transplantation with allogeneic bone marrow. Such infections are associated with graft-versus-host disease and the corticosteroids used in its control, the use of a mis-matched, unrelated, or T-lymphocyte depleted allogeneic transplant. Laboratory studies have shown that GM-CSF and γ-interferon can reverse the effect of dexamethasone on the responsiveness and killing activity of monocytes exposed to *A. fumigatus* hyphae.
A clinical trial is now under way on the effect of GM-CSF in reducing fungal infections in patients with graft-versus-host disease receiving long term corticosteroids.

Both G-CSF and GM-CSF have been shown to increase numbers of granulocytes 3-8 fold when given the normal donors prior to aphoresis. Raised neutrophil counts can persist for 24 hours or longer, and the use of "enhanced" transfusions may offer additional protection as an adjunct to antifungal therapy in high risk patients.

G-CSF, GM-CSF and M-CSF have been shown to reduce the severity of mucositis arising from chemotherapy, radiotherapy or herpes infections. Mucosal growth factors such as keratinocyte growth factor and transforming growth factor also reduce mucosal damage, and are being evaluated in clinical trials.

Session VIII

chaired by
Mahmoud A. Ghannoum

Laboratory-clinical correlations

The final session focused on «Laboratory-clinical correlations» and was introduced by Michael A. Pfaller (Iowa City, Iowa), who spoke on «The current status and future development of antifungal susceptibility testing». Last year, a standardised broth dilution test for testing the antifungal susceptibility of yeasts was introduced by the NCCL Subcommittee specially appointed for this purpose. This represented 15 years of cooperative effort. Publication of quality control limits for five antifungal agents and the provision of interpretative MIC breakpoints for three of them has provided useful parameters for surveying clinical isolates of *Candida*. More precise investigations are now feasible into correlations between MIC values and outcomes of infection, and for surveillance studies at national and international levels. Antifungal testing is now at a stage comparable to that of antibacterial testing.

New developments include an improved version of the M27 microdilution method, and the introduction of two commercially produced colorimetric tests (Sensitre and KPI). The Etest is also being further developed: it appears to be of value as an alternative to the reference method, and also seems promising for the testing of moulds.

Availability of a standardised method makes proficiency testing practicable, and antifungal susceptibility testing is now included in the quality control programme of the American College of Pathologists. Some 50 laboratories participated in 1997. It is intended that in following years, that proficiency testing will involve all new antifungals, and that the availability of such tests for future clinical trails should make it possible to determine clinical correlates or breakpoints for individual agents. Future attention will also focus on improved ability to detect ampho-

tericin B resistance, production of a NCCL procedure for susceptibility of moulds, and applications of reference procedures to the testing of dermatophytes.

William G. Merz (Baltimore, Maryland), speaking on «Clinical laboratory pearls for the clinician as relates to mycotic disease», analysed the effects on isolation rates of fungi from blood culture systems, when incubation time was reduced and blind subcultures eliminated. Such changes may be encouraged in the name of economy, but are likely to reduce the value of blood cultures in diagnosing fungal infections. Data from Johns Hopkins Hospital showed that although reduction of incubation by 2 days had no significant effect on the isolation rate of bacteria, this was not the case for fungi. After incubation for 5 days, 15 isolates of yeasts (*C. albicans*, *C. parapsilosis*, *C. glabrata* and *C. neoformans*) were recovered from almost 4,000 blood cultures. Extension of incubation to the normal 7 days picked up another 3 yeasts, whilst blind subcultures increased the number of isolations by another 7. Thus, there was a 26% increase in the number of fungal isolates if the original culture procedures were used. Other data have shown that between 30-40% of positive blood cultures for *C. neoformans* would have been missed, if blind subculturing had been omitted.

Individual case histories were presented, emphasising the importance of appropriate laboratory procedures. The first was a widespread infection with *Paecilomyces lilacinus* in a patient 4 months after an autologous bone marrow transplant. Only two blood cultures were positive, by metabolic signal, 4 others requiring extended incubation. The organism was grown only after 10 days of incubation. The second case involved infection of skin grafts with *Rhizopus oryzae* in a patient who had received a heart transplant.

The importance of communication between clinic and laboratory was emphasized. It greatly improves the possibility of arriving at a diagnosis.

Michael A. Saubolle (Phoenix, Arizona) then considered «Good mycology: identification of fungi to species level; how important is it to the clinician?». By reference to specific examples, an attempt was made to distinguish between situations where identification is important, and where it makes little real difference to the course of management. Distinction between *C. albicans* and *C. dubliniensis* may have clinical relevance, for the latter species, although similar to *C. albicans* is found only in patients with AIDS, and has a greater innate resistance to fluconazole. New laboratory procedures, such as gene probes, have been introduced, and facilitate identification of important pathogens such as *H. capsulatum*, *B. dermatitidis* and *C. immitis*. However, a major consideration of such procedures is cost effectiveness. They provide answers, but are the costs justified? It was suggested that relevant questions to be considered are does identification provide 1) a diagnosis? and 2) information of clinical relevance? In some cases, management is based on histopathological findings alone, and is unaffected by more precise laboratory identification.

Areas where full identification may be important include diagnosis, assessment of prognosis, epidemiology, and therapeutic implications.

The final lecture was by Richard F. Hector (San Francisco, California), who spoke on «The fascinating history of a protean mycosis - coccidioidomycosis». The subject was reviewed on the basis of the individuals who contributed towards an understanding of the natural history of the disease and its causal agent. Amongst those whose contribution was singled out were Drs. Rixford, Gilchrist, Ophüls, Moffitt, Dickson, Smith, and Gifford.

The 9th Focus meeting will be held in San Diego, California.

Mycology Courses in Europe (1999)

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: Three months (one full day/week) - February to April
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 - April 5-12, 1999
Hours theory/practice: Theory 50h / practice 20h
Admitted participants: 10
Certificate: Diploma

FRANCE

Cours de Mycologie Médicale ***(every year)***

Organizers: Dr. Cl. de Bièvre (director of the course), 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 26-June 18, 1999
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)*

Organizer: Dr. K. Tintelnot, Robert-Koch-Institut, Bundesgesundheitsamt, Nordufer 20, 13353 Berlin
Address: Working Group "Clinical Mycology" of DMykG, Fax +33 1 45688218
Duration - date: One day - January 29, 1999
Hours theory/practice: Only theory
Admitted participants: 25
Scientific programme: Antimycotic susceptibility tests. Identification of yeasts. Immunological diagnostic of candidose opportunistes. *Aspergillus*

Course on Experimental Mycology *(every year)*

Organizer: Dr. H.-J. Tietz, Zahnarzt, Facharzt für Mikrobiologie, Hautklinik der Charité, Schumannstr. 20/21, 10117 Berlin
Address: Working Group "Micological Laboratory Diagnostics" of DMykG
Date: Autumn 1999
Hours theory/practice: Only theory
Admitted participants: 30
Scientific programme: Identification of yeasts and dermatophytes

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 6-10, 1999
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 - May 5-7, 1999
Admitted participants: 10
Hours theory/practice: Theory 12h / practice 10h
Certificate: Diploma

SPAIN

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

Organizer: Dr. Josep M. Torres-Rodriguez, Unitat de Microbiologia, Institut Municipal D'Investigació Mèdica, C/ Aiguader 80, 08003 Barcelona, Fax +34 93 221 3237
Address: Departamento de Microbiologia, Fac. Medicina "UDIMAS", Universidad Autonoma de Barcelona
Duration-date: Three weeks - February 1999
Hours theory/practice: Theory 65% / practice 35%
Admitted participants: 15
Certificate: Diploma

THE NETHERLANDS

Course on Medical Mycology ***(Dutch language edition)***

Organizer: Centraalbureau voor Schimmelcultures, Baarn
Address: CBS, Oosterstr. 1, 3742 SK Baarn Fax +31 3554 16142
Duration - date: Three weeks - April 1999
Admitted participants: 25
Scientific programme: Biodiversity in medical mycology. All major species and their clinical pictures are treated
Certificate: Diploma

Course on General Mycology ***(English language edition)***

Organizer: Centraalbureau voor Schimmelcultures, Baarn
Address: CBS, Oosterstr. 1, 3742 SK Baarn Fax +31 3554 16142
Duration - date: Three weeks - April 6-24, 1999
Hours theory/practice: Theory 30h / practice 75h
Admitted participants: 25
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 Dagnostic Medical Mycology

Organizer: British Society for Medical Mycology (Prof. E.G.V. Evans and Dr. H.R. Ashbee)
Address: PHLS Mycology Reference Laboratory, Department of Microbiology, University of Leeds, Leeds LS2 9JT
Duration - date: Five days - April 12-16, 1999
Hours theory/practice: Theory 15h / practice 17.5h
Admitted participants: 50; mainly laboratory technical staff
Scientific programme: Course of lectures, practical and informal discussion on topics in diagnostic medical mycology

(Information provided by the member Societies)