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History of Medical Mycology

File 4 (1983-Dedication)

1983

Kyung-Joo Kwon-Chung, at the National Institutes of Health (N.I.H.), Bethesda, Maryland, U.S.A., and Gerard De Vries, of the Centraalbureau voor Schimmelcultures (C.B.S.), the Netherlands, reported the results of their studies on a feline isolate of a phaeoid fungus characterized by morphological features strictly fitting, in their opinion, the description made by Pier Andrea Saccardo of the original Guido Banti's isolate (1983). They stated that the cat isolate differed from Chester W. Emmons *Cladosporium trichoides* with reference to "conidial size, branching of conidial chains and minimum, optimum and maximum temperature for growth". Although these were the issues that had been rejected by Michael R. McGinnis and Dante Borelli (1981), Kwon-Chung and De Vries claimed that "*Cladosporium bantianum* (Saccardo) Borelli and *C. trichoides* Emmons should be regarded as two separate species" [Ajello, 1998; Kwon-Chung and de Vries, 1983; McGinnis and Borelli, 1981].

1984

Opposed conclusions were achieved by Shozo Honbo, Paul G. Standard, Arvind A. Padhye, Libero Ajello and Leo Kaufman (1984) at the Centers for Disease Control (C.D.C.) in Atlanta, Georgia, U.S.A., using monospecific sera by the exoantigen test procedure. They

reported that “all human and cat isolates of *Cladosporium bantianum* and *C. trichoides* were found to share the same antigens”. According to these results, the statement claimed by Kwon-Chung and De Vries (1983) should be considered invalid [Ajello, 1998; Honbo et al., 1984; Kwon-Chung and de Vries, 1983].

George J. Hageage and Brian J. Harrington, from the Department of Pathology, University of Massachusetts Medical Center, Worcester, Massachusetts, U.S.A., reported that “Calcofluor white”, a fluorochrome with affinity for chitin and cellulose, could be useful to reveal fungal elements in clinical samples (1984). The use of Calcofluor white allowed to overcome some inefficiencies encountered with the use of KOH preparations although being more rapid of specific fungal staining techniques such as PAS and Gomori [Espinel-Ingroff, 1996; Hageage and Harrington, 1984].

Description of:

Hortaea werneckii (Horta) Nishimura & Miyaji, 1984

1985

Bruce L. Miller, Karen Y. Miller and William E. Timberlake, from the Department of Plant Pathology, University of California, Davis, California, U.S.A., succeeded to replace genes of *Aspergillus nidulans* with mutant alleles made *in vitro* (1985) by using either the one- or two-step methodology described for *Saccharomyces cerevisiae* by Stewart Scherer and Ronald W. Davis, from the Department of Biochemistry, Stanford University School of Medicine, Stanford, California (1979). This technological approach could allow either the rapid proof of the identity of new genes isolated by complementation of mutations or the investigation of the biochemical and biological consequences deriving from the introduction of a specific, preselected mutation into the genome of otherwise unaltered cell [Espinel-Ingroff, 1996; Miller et al., 1985; Scherer and Davis, 1979].

Bernice Slutsky, Jeffrey Buffo and David R. Soll, from the Department of Biology of the University of Iowa, Iowa City, Iowa, U.S.A., showed that *Candida albicans* can hereditarily and reversibly switch with high frequency through different phenotypes characterized by the white/opaque morphology of the colonies grown on agar media (1985). This observation supported the hypothesis that the phenotypic switching occurring in *C. albicans* and other fungi could be related to such important features as invasiveness, organ tropism, immunoevasion and drug resistance. Among the genes regulated by switching in *C. albicans*, Brian T. Morrow, Thyagarajan Srikantha and David R. Soll, from the Department of Biology of the University of Iowa, identified *PEP1*, encoding an acid protease of the pepsinogen family, *Op1a* (1992), which is located on a different chromosome than *PEP1*, and the white-specific gene *Wh11*, which is not transcribed in opaque cells (1993) [Espinel-Ingroff, 1996; Morrow et al., 1992; Slutsky et al., 1985; Srikantha and Soll, 1993].

Stuart M. Levitz and Richard D. Diamond, of the Evans Memorial Department of Clinical Research and the Department of Medicine, University Hospital, Boston University Medical Center, Boston, Massachusetts, U.S.A., reported that, in addition to their natural features, resting conidia of *Aspergillus fumigatus* were highly resistant within neutrophils because of their capacity to stimulate a suboptimal release of oxidative and nonoxidative fungicidal products (1985). Levitz and his coworkers, M.E. Selsted, T. Ganz, R.I. Lehrer and R.D. Diamond, showed that antimicrobial cationic peptides (defensins) from rabbit neutrophils and macrophages were not able to kill dormant conidia of *A. fumigatus* and *Rhizopus arrhizus* (as *R. oryzae*) (1986). Once the filamentous form of these fungi was developed, however, phagocytic cells and their cationic peptides could display their fungicidal activity [Espinel-Ingroff, 1996; Levitz and Diamond, 1985; Levitz et al., 1986].

1986

Michael R. McGinnis, Dante Borelli, Arvind A. Padhye and Libero Ajello ascertained that *Cladosporium bantianum* was a thermotolerant fungus (1986). Guido Banti (1911) had noticed that his original isolate grew at 37 °C and, not surprisingly, it was pathogenic for rabbits whose physiological body temperature is 40 °C. Borelli had verified that strains of *C. bantianum* could grow at 42-43 °C. The common properties of thermotolerance and neurotropism exhibited by the original isolates of *C. bantianum* and *C. trichoides* provided support to the conspecificity of these two taxa [Ajello, 1998; McGinnis et al., 1986].

This long dispute concerning the taxonomy of the Guido Banti's isolate had a further impulse when Michael R. McGinnis, Dante Borelli and Arvind A. Padhye (1986) reclassified *Cladosporium bantianum* into the genus *Xylohypha* (Fries, 1753) as *X. bantiana* (Saccardo, 1912) McGinnis, Padhye, Borelli & Ajello, 1986. The new combination was considered appropriate because “*Xylohypha bantiana* produces conidiophores that are indistinguishable from its vegetative hyphae and one-celled, smooth-walled conidia that are borne in long, infrequently branched chains. The blastoconidia do not possess darkly pigmented hila. In contrast, members of the genus *Cladosporium* Link produce erect, distinct conidiophores and one- to four-celled smooth-to-rough-walled conidia that occur in short, frequently branched, fragile chains. The blastoconidia have darkly pigmented hila. *Cladosporium trichoides* Emmons is a later synonym of *X. bantiana*” [Ajello, 1998; McGinnis et al., 1986].

The publications of Donald M. Griffin (1960) and Phyllis M. Stockdale (1961) were propaedeutic to the discovery of the perfect states of other members of the genera *Microsporum* and *Trichophyton*. While the teleomorphs of the *Microsporum* species were left in the genus *Nannizzia*, the ones of the *Trichophyton* species were classified in the genus *Arthroderma*. As more perfect states were described in the two genera, the distinction between the two *taxa*, however, became increasingly tenuous, particularly with reference to the intergradations of their peridial hyphae. A close genetic relationship between the two

genera, moreover, was disclosed by mating studies. Irene Weitzman, Michael R. McGinnis, Arvind A. Padhye and Libero Ajello, at the Mycology Division of the Centers for Disease Control (C.D.C.), Atlanta, Georgia, U.S.A. (1986), on the basis of critical comparative studies, suggested that the genus *Nannizzia* be considered as a later synonym of the genus *Arthroderma*. Nowadays, all the teleomorphs of the *Microsporum* and *Trichophyton* species are classified in the genus *Arthroderma* (Curry, 1860) Weitzman, Mc Ginnis, Padhye & Ajello, 1986 [Ajello, 1998; Griffin, 1960; Stockdale, 1961; Weitzman et al., 1986].

1987

Françoise Dromer, Jeannine Charreire, Alain Contrepois, Claude Carbon and Patrick Yeni, at the Laboratoire des Infections Expérimentales, Institut National de la Santé et de la Recherche Médicale U13, and U283 (Laboratory of Experimental Infections, National Institute of Health and Medical Research), Paris, France, showed that a monoclonal antibody to *Cryptococcus neoformans* polysaccharide was protective against experimental cryptococcal infection in mice (1987). As the question of whether specific antibodies could protect against fungal pathogens was considered controversial, the landmark paper of Dromer and collaborators, as well as dozens of subsequent studies, have established conclusively that certain antibodies are effective against fungi [Casadevall, 1995; Dromer et al., 1987].

As a postdoctoral student at the Centers for Disease Control (C.D.C.), Atlanta, Georgia, U.S.A., Timothy J. Lott, together with Patrick Boiron and Errol Reiss, defined, by field inversion gel electrophoresis, an electrophoretic karyotype for *Candida albicans* (1987). The result from the migration of intact chromosomes was considered as species specific within the genus *Candida*, thus introducing to the field of molecular fungal epidemiology by other more sensitive techniques as described by Scherer and Stevens [Espinel-Ingroff, 1996; Lott et al., 1987; Scherer and Stevens, 1987].

Description of:

Pythium insidiosum De Cock, Mendoza, Padhye, Ajello & Kaufman, 1987

1988

James E. Cutler, now Professor of Microbiology & Immunology Parasitology, Tulane University, and Associate Director of the Research Institute for Children at Children's Hospital, New Orleans, Louisiana, U.S.A., in collaboration with Pati M. Glee and Harold L. Horn, of the Department of Microbiology, Montana State University, Bozeman, Montana, U.S.A., isolated a DNA probe, hybridizing specifically with the DNA from *Candida albicans* (and *C. stellatoidea*) but not with the one from other infectious agents or from the host, that proved to be effective in clinical samples, thus introducing to the field of diagnostic molecular Medical Mycology [Cutler et al., 1988; Espinel-Ingroff, 1996].

Richard A. Calderone, Professor and Chairman, in collaboration with Lisa Linehan, and Elsa Wadsworth at the Department of Microbiology and Immunology, Georgetown University, Washington D.C., U.S.A., and Ann L. Sandberg, of the National Institute of Dental Research, Bethesda, Maryland, U.S.A., worked on the characterization of the receptors on *C. albicans* that bind complement. In hyphal extracts of the yeast they characterized two protein receptors, iC3b (7 kDa) and C3d (60kDa), which bound the relative C3 fragments of complement thus supporting the idea of their pathogenetic role (1988) [Calderone et al., 1988; Espinel-Ingroff, 1996].

Beatrice B. Magee, and Paul T. Magee, at the Department of Genetics and Cell Biology, University of Minnesota, St. Paul, Minneapolis, Minnesota, U.S.A., in collaboration with Yigal Koltin, and Jessica A. Gorman, speculated that *C. albicans* possessed seven chromosomes to which genes were assigned by hybridization (1988). In the following years, other studies on karyotypes have estimated from six to nine the number of chromosomes in

the same yeast. Brian L. Wickes, of the Laboratory of Clinical Investigation, National Institutes of Health (N.I.H.), Bethesda, with Jeff Staudinger, Beatrice B. Magee, Kyoung-Joo Kwon-Chung and Paul T. Magee, by using more sophisticated techniques of pulsed-field electrophoresis and studies of genetic linkages, stated that the factual number of chromosomes for *C. albicans* was eight (1991). The previous wrong count of seven was attributed to the failure to separate the two largest chromosomes (chromosome R including the rDNA genes and chromosome 1) [Espinel-Ingroff, 1996; Magee et al., 1988; Wickes et al., 1991].

1992

The Federazione Italiana di Micopatologia Umana ed Animale (Italian Federation for Human and Animal Mycopathology) (F.I.M.U.A.), was established in Florence, Italy (1992) from the merger of two independent mycological Societies based in the late '80s: Società Italiana per la Micologia Umana ed Animale (Italian Society for Human and Animal Mycology) (S.I.M.U.A.) and Associazione Italiana di Micopatologia (Italian Association of Mycopathology) (A.I.M.P.). The aim of the Society was to promote updates in the mycological field, organizing courses, seminars, and, every two years, the National Congress (www.fimua.it).

Kyoung-Joo Kwon-Chung and John Bennett, in their textbook “Medical Mycology” (1992), confirmed that “*Cladosporium trichoides* and *C. bantianum* are not the same fungus” It was also claimed that the new classification of *C. bantianum* into the genus *Xylohypha* should be rejected on the basis of conidial morphology. This statement was affirmed by Kwon-Chung, and Brian L. Wickes of the Clinical Mycology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health (N.I.H.), Bethesda, Maryland, U.S.A., and James Plaskowitz, of the Systematic Botany, Mycology and Nematology Laboratory, United

States Department of Agriculture, Beltsville, Maryland, who sustained that *C. bantianum* was dissimilar from *C. trichoides* (1989). Fundamental differences, moreover, were reported between the investigated isolates of *Xylohypha nigrescens* and *Cladosporium* spp. in respect to colony morphology, conidiogenesis and conidial morphology. Their conclusion was that the Guido Banti's and Chester W. Emmons' isolates were two distinct entities and that transfer of *C. trichoides* to the genus *Xylohypha* was not justified [Ajello, 1998; Kwon-Chung and Bennett, 1992; Kwon-Chung et al., 1989].

Elmer P. Brummer, of the Department of Medicine, Santa Clara Valley Medical Center, San José, California, U.S.A., in collaboration with Purushothama R. Bhagavathula, Linda H. Hanson and David A. Stevens, studied the *in vitro* interaction between macrophages and azoles (itraconazole and ketoconazole) against *Blastomyces dermatitidis* (1992). They reported that fungistatic concentrations of itraconazole might act synergistically with murine peritoneal macrophages to kill this fungus [Brummer et al., 1992; Espinel-Ingroff, 1996].

Kyoung-Joo Kwon-Chung, and Bryan L. Wickes, of the Clinical Mycology Section, National Institute of Allergy and Infectious Diseases, Bethesda, in collaboration with Jeffrey C. Edman, separated by pulsed-field electrophoresis the chromosomes of the type cultures of *Filobasidiella neoformans* var. *neoformans* and the tester *Cryptococcus* strains (type *a* and type α). They stated that different karyotypes occurred in the two mating types. Studies of mated congenic strains carried out in mice demonstrated that type α was more virulent than type *a* [Espinel-Ingroff, 1996; Kwon-Chung et al., 1992].

1993

The European Confederation of Medical Mycology (E.C.M.M.) was instituted (1993) at the Institut Pasteur in Paris, France, with the statement that "Its basic aims are to facilitate scientific exchanges, to improve communication between European mycologists, to create

study groups for the standardization of methodology, to coordinate multicentre drug trials, to investigate the epidemiology of mycoses, to undertake other appropriate activities, and to meet annually in turn in each country at a European Congress...” [Bastide et al., 1993].

The Australian Mycological Society was established (1993) and was incorporated in the Australasian Mycological Society (A.S.M.) located in Otago, New Zealand (1995). The Society, publishing the official journal “The Australasian Mycologist”, is governed by rules specified in the constitution and aimed at the object to promote the study of fungi.

1995

The long controversy concerning the taxonomy of the Banti’s fungus came to an apparent conclusion when Sybren G. de Hoog, a Dutch mycologist of the Centraalbureau voor Schimmelcultures (C.B.S.), Utrecht, The Netherlands, published with Eveline Guého and Florence Masclaux, of the Mycology Service at the Institut Pasteur in Paris, France, Bert Gerrits Van den Ende, of the C.B.S., Kyoung-Joo Kwon-Chung, of the Clinical Mycology Section, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, U.S.A., and Michael R. McGinnis, of the University of Texas Medical Branch, Galveston, Texas, U.S.A., the results of their cumulative studies on the nutritional physiology and molecular biology of human pathogenic species of the genera *Cladosporium* and *Xylopyha*. They stated that the valid name for Pier Andrea Saccardo’s *Torula bantiana* should be *Cladophialophora bantiana* (Saccardo 1912) de Hoog, Kwon-Chung et McGinnis 1995 [de Hoog et al., 1995].

The first edition of “Atlas of Clinical Fungi” was published in 1995 by Sybren G. de Hoog (C.B.S.) and Josep Guarro (Mycology Unit, Medical School, Institut d’Investigació Sanitària Pere Virgili, Rovira i Virgili University, Reus, Spain). In the second (2000) and following editions, including electronic ones (third edition, 2011), two more authors, Josepa Gené (Mycology Unit, Medical School, Institut d’Investigació Sanitària Pere Virgili, Rovira i

Virgili University) and Josè M. Figueras (Unit of Microbiology, Department of Basic Health Sciences, School of Medicine and Health Sciences, Rovira i Virgili University), joined them [de Hoog and Guarro, 1995; de Hoog et al., 2000].

Description of:

Candida dubliniensis Sullivan, Westerneng, Haynes, Bennett & Coleman, 1995

1999

Description of:

Cryptococcus neoformans (Sanfelice) Vuillemin var. *grubii* Franzot, Salkin & Casadevall, 1999

2002

Matthew C. Fisher of the Institute of Zoology, London, U.K., and John W. Taylor, of the Department of Plant and Microbial Biology, University of California at Berkeley, Berkeley, California, U.S.A., together with Gina L. Koenig and Thomas J. White, of the Roche Molecular Systems, Alameda, California, U.S.A., distinguished *Coccidioides posadasii* from *C. immitis* within the genus *Coccidioides* by using microsatellites as useful phylogenetic markers. These two species were morphologically identical but genetically and epidemiologically distinct. *Coccidioides immitis* was considered to be geographically limited to California's San Joaquin valley, U.S.A., whereas *C. posadasii* was located in the remaining semi-arid areas in the southwest of the United States, Mexico, Central and South America. *Coccidioides posadasii* Fisher, Koenig, White & Taylor, 2002, was probably first discovered in Argentina by Alejandro Posadas, after whom the fungus is named, visiting the patient who had the first documented case of coccidioidmycosis (1890) [Fisher et al., 2002].

2005

Antonella Torosantucci, Carla Bromuro, Paola Chiani, Flavia De Bernardis and Antonio Cassone, of the Department of Infectious, Parasitic and Immune-mediated Diseases, Istituto Superiore di Sanità (I.S.S.), Rome, Italy, Luciano Polonelli, of the Microbiology Section, Department of Pathology and Laboratory Medicine, University of Parma, Parma, Italy, Francesco Berti, Chiara Galli, Francesco Norelli, Cinzia Bellucci, Paolo Costantino, Rino Rappuoli, of Chiron Vaccines, Siena, Italy, generated the first vaccine able to protect against a variety of human pathogenic fungi, (*Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*). The “universal” antifungal vaccine was constituted by β -glucan preparation from the brown alga *Laminaria digitata* conjugated to the diphtheria toxoid. Based on early studies of Antonio Cassone and Flavia De Bernardis, of the Istituto Superiore di Sanità (I.S.S.), Rome, and Luciano Polonelli and Stefania Conti, of the University of Parma, showing that universal fungal targets can induce fungicidal antibodies (1997), cross-protection was directly mediated by anti- β -glucan antibodies, as proven *in vitro* in the absence of immune-effector cells, thus introducing “a fungal heresy into immunological dogma” [Casadevall and Pirofski, 2007; Cassone et al., 1997; Rachini et al., 2007; Torosantucci et al., 2005].

2008

Fèlix Gilgado, Josep Cano, Josepa Gené, and Josep Guarro, of the Microbiology Unit, University Rovira i Virgili, Reus, Spain, in collaboration with Deanna A. Sutton, of the Fungus Testing Laboratory, Department of Pathology, The University of Texas Health Science Center, San Antonio, Texas, U.S.A., on the basis of morphological, physiologic, and molecular studies involving numerous isolates of *Pseudallescheria boydii* and *Scedosporium apiospermum* demonstrated that they should be considered different species. The new name

Scedosporium boydii was therefore proposed for the anamorph of *P. boydii*. Their findings also led to proposal of a new species, *Scedosporium dehoogii* [Gilgado et al., 2008]. Further studies (2010) of the same authors on isolates of *S. apiospermum* allowed the description of its teleomorph, the new species *Pseudallescheria apiosperma* [Gilgado et al., 2010].

Description of:

Sporothrix luriei (Ajello & Kaplan) Marimon, Gené, Cano & Guarro, 2008

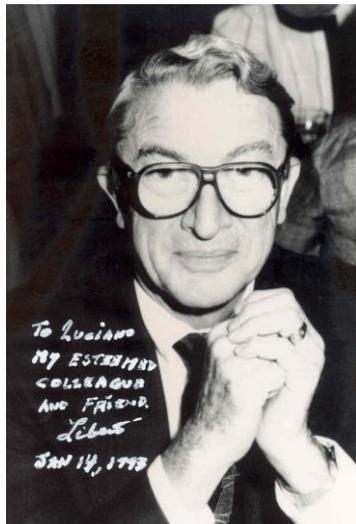
Today and tomorrow

Milestones in Medical Mycology from the beginning until today have been so many that some important contributions may have been omitted or others may have been emphasized due to personal ignorance or assessment. The scientific progresses achieved in Medical Mycology along the years, however, have promoted effects well beyond the specific discipline, stimulating the interest of researchers in Microbiology, Medicine, Biology, Genetics, and Immunology. Although the history of Medical Mycology dated back almost two hundreds years, the oldest in Medical Microbiology and Virology, much remains to be understood about mycoses and their etiologic agents. Criticities in the control of fungal infections concern the development of markers for the early diagnosis and monitoring, antibiotics, for the treatment and prophylaxis, immunomodulators, for resistance and omeostasis, vaccines, for prevention and therapy. The task to prosecute the work performed by the founders is delegated to the new generations of scientists and, in particular, to those so talented and enthusiastic to further advance the knowledge of Medical Mycology.

Dedication

This “History of Medical Mycology” is dedicated to Dr. Libero Ajello, who was not only a great medical mycologist but also a rare embodiment of science and humanity. His parents

had emigrated to U.S. from Petralia Sottana, a village in the province of Palermo, Sicily, Italy, and he has always been proud of his origins. Libero in Italian means “free”, free as the birds that he loved to watch in the wild. The original author, Luciano Polonelli, is honored to have been regarded by him first as a pupil and then as a friend. The hope is that, as his personal homage, this history is continuously emended by current and future medical mycologists, in order to keep Libero Ajello’s memory always alive as our beloved science.



Dr. Libero Ajello (1916-2004)