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Collaborative Translational Research and Control of Meningitis in Sudan

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Sudan lies within the meningitis belt and meningococcal disease has been one of its major problems throughout the twentieth century. Over 12,000 and 55,000 cases were recorded in the years 1935 and

1950 respectively; and during the period 1968-1980, over forty thousands (40,513) were inflicted with the disease of whom 1,220 have died. A collaborative translational research between the Uni- versity of Khartoum and Uppsala University in Sweden managed to document the epidemiology, clinical features and complications of childhood acute bacterial meningitis (ABM) in Sudan during both an inter-epidemic (endemic) period (1985-1986), and the 1988 serogroup A epidemic; and to examine the phenotypic and genetic similarities and differences of Neisseria meningitidis strains isolated in Sudan and Sweden. A novel enzyme immunoassay test (Pharmacia Meningitis EIA-Test) was evaluated as a potential rapid diagnostic method for the detection of Haemophilus influenzae (HI) type b, Neisseria meningitidis (MC) and Streptococcus pneumoniae (PNC). The test was found to have good sensitivity (0.86) and specificity (0.95) in the inter-epidemic period; and to be adaptable to the field work in Sudan during the 1988 MC epidemic. During inter-epidemic (endemic) situations in Sudan, >90 % of childhood ABM was caused by one of the three organisms, HI type b, MC and PNC. HI accounted for 57% of the cases. The peak incidence (76%) of HI cases was in infants (<12 months) similar to the situation in other African countries. The overall case fatality ratio was 18.6%.

Prospective follow-up of survivors for 3-4 years revealed that an additional 43% either died or had permanent neurological complications, the most prevalent and persistent of which was sensorineural hearing loss recorded in 22% of long term survivors. Post-meningitic children were found to have significantly lower intelligence quotients (92.3 ± 13.9) than their sibling controls (100.7 ± 10.2, P=0.029). Features of the large serogroup A sulphonamide resistant MC epidemic (February-August

1988) in Khartoum were documented. An estimated annual incidence of 1,679/100,000 was recorded at the peak of the epidemic. The highest attack rate was in young children <5 years, as in many other African countries; nevertheless, a high morbidity was observed in adults (31% of the cases > or = 20 years). The clinical features, mortality (6.3%) and short term sequelae in Sudanese children were generally within the framework described for MC disease elsewhere.

Detailed analysis of MC isolates from Sudan and Sweden by characterizing their electrophoretic enzyme types, DNA restriction endonuclease pattern and outer membrane proteins, revealed that serogroup A MC clone III-1 was responsible of The Sudan epidemic in 1988 and has been the dominant serogroup A organism in Sweden since 1973. The Sudanese strains isolated prior to the epidemic (1985) were clone IV-1. Clone III-1 has caused two global pandemic waves within three decades and clone IV-1 has been resident in the meningitis belt for 25 years. This collaborative translational research paved the way for the successful control of acute bacterial meningitis following the introduction of conjugate vaccines.

The Era of Pediatric Neurogenetics

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Following the successful implementation of the Expanded Program on Immunization worldwide, and with the improvement in childhood nutrition, genetic diseases emerged as a significant health problem causing significant mortality and life-long morbidity. The majority of these genetic disor- ders manifest in childhood with either neurobehavioural impairment or as degenerative neurological disorders.

The high incidence of consanguineous marriages in North Africa, including Sudan, and the Arabian Peninsula is reflected on the high prevalence of autosomal recessive (AR) disorders, in contrast to the situation in North America and Europe. The magnitude of neuromuscular disorders, mostly inherited as AR, is apparently large. The prevalence rate of anterior horn cell diseases, including Werdnig-Hoffman disease, was 133 and 177 per million in two studies, compared to 12 per million from the World Survey. A severe childhood autosomal recessive muscular dystrophy (SCARMD) resembling Duchenne MD was first noted in families from Sudan and Tunisia. Subsequently, the disease was identified in other Maghreb countries and in the Arabian Peninsula. The frequency of this form of MD was found to be equivalent to, and higher than, Duchenne MD in Tunisia and Saudi Arabia, re- spectively. The corresponding genes were identified including alpha-sarcoglycan (or Adhalin gene, from the Arabic word Adhal for muscle). The same founder mutation of one form of congenital muscular dystrophy (MDC1A) was detected in families from Saudi Arabia and Sudan.

Utilizing the power of family-based genetic studies combined with emerging DNA technology, new syndromes and diseases were identified. Those with gene / locus identification included:

1. Salih myopathy: Autosomal recessive titinopathy causing early onset myopa- thy/ dystrophy with dilated cardiomyopathy. (http:// www.ncbi.nlm.nih.gov/books/ NBK83297/).
2. Charcot-Marie-Tooth Disease Type 4B1 (OMIM 601382).
3. A new form of childhood-onset, autosomal recessive spinocerebellar ataxia and epi- lepsy. (http://brain.oxfordjournals.org/cgi/content/ full/130/7/1921). (http://www. ncbi.nlm.nih. gov/pubmed/24369382).
4. Spinocerebellar ataxia with axonal neuropathy (SCAN1; OMIM 607250); http://www.ncbi. nlm.nih.gov/books/NBK1105/).
5. Horizontal gaze palsy and progressive scoliosis (OMIM 607313).
6. Bosley-Salih-Alorainy syndrome (OMIM 601536).
7. Salih ataxia: (http://brain.oxfordjournals.org/ content/133/8/2439.full.pdf+html) (http:// www.ncbi.nlm.nih.gov/pubmed/23728897).
8. A new form of childhood-onset autosomal recessive hereditary spastic paraplegia (SPG49) caused by a novel gene (CYP2U1) mutations. (http://www.cell.com/AJHG/ abstract/S0002-9297%2812%2900579-4).
9. A novel form of congenital myasthenic syndrome due to AL2G2 gene mutations (http://brain.oxfordjournals.org/ content/136/3/944.long).
10. A novel form of congenital muscular dystrophy due to B3GALNT2 gene mutations (http://www.cell.com/AJHG/retrieve/pii/ S0002929713000694).

11. A newly recognized autosomal recessive syndrome affecting neurologic function and vision. (http://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.35850/abstract;jsessi oni d=57FC0B56AA5ACBFD4CD5CEFA85862B3C.d01t01).

12. A novel gene for migrating partial seizures in infancy. (http://www.ncbi.nlm.nih.gov/pubmed/24596948).

Household Air Pollution

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These advances of pediatric neurogenetics helped in refashioning the prognosis and differential diagnosis of these diseases. It also made possible the choice of life-saving drugs in congenital myasthenic syndromes, and made possible presymptomatic, prenatal, and pre-implantation genetic diagnoses for affected families.

Household air pollution from the use of biomass fuels is a major public health hazard affecting over

3 billion people living in developing countries most of whom are women and children. In Sudan the national burden of disease attributed to biomass fuel use is estimated to be 0.7% but may be significantly higher as this is an estimate based on estimates of exposure. Biomass fuel combustion releases many toxic pollutants which are damaging to the respiratory tract, the cardiovascular and neurologic systems and are associated with low birth weight and fetal wastage. Household air pollution has been studied primarily by using devices which measure exposure in dwellings and on the clothes of the residents. These devices measure the most important pollutants, carbon monoxide, sulfur dioxide, and particulate matter. Although inhaled sulfur dioxide and particulate matter damage the lungs, only carbon monoxide is systemically absorbed and only carbon monoxide can be measured in the body. In this paper, we will review the pathophysiology of carbon monoxide poisoning and report some preliminary results of the study which we, Prof. Suliman and our colleagues from Sudan car- ried out immediately prior to this conference.

Challenges and opportunities for the development of new treatments for leishmaniasis

Prof. Simon L. Croft

Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, UK

There are significant differences in the progress and approaches to drug development for visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL). VL, caused by L. donovani and L. infantum, is potentially fatal and is the primary focus for drug R & D. The need for new drugs is urgent as the standard pentavalent antimonials are now almost obsolete in the key endemic area in Bihar state, India due to resistance. A number of amphotericin B lipid formulations have proved effective in the treatment VL, although only the liposomal formulation, AmBisome®, has become a standard treat- ment and demonstrated efficacy in single dose treatment and in combination therapy. Major challenges remain for VL treatment due to regional differences in response rates, and co-infections with HIV. Despite extensive screening and evaluation projects, few safe, oral, short course, cheap drugs

are close to clinical development.

There are limited treatment options for CL. One problem is the variation in drug effectiveness across the different Leishmania species that cause CL. Two recent Cochrane analyses of clinical trials of CL emphasized that most clinical studies did not meet standards of randomized placebo controlled trials. One promising approach has been the development of topical formulations, so far most successful for paromomycin. Another approach to CL treatment is to accelerate self-cure through the use of immunomodulators as adjunct therapies, for example, imiquimod.

All attempts to discover and develop novel drugs for neglected infectious diseases depend on a network of partnerships, upon involvement of PDPs and the pharmaceutical industry and the involvement of key players in disease endemic countries. The issues of changing patterns of funding and involvement of different sectors all play a part in bringing new treatments to patients.

Potentials for research collaboration in infectious and tropical diseases

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The need for new drugs, diagnostics and vaccines has changed over the past decade for many of neglected infectious diseases (NIDs). NIDs can be viewed in three categories: (a) those for which there is some market, some commercial and public health incentive, eg. malaria and tuberculosis, (b) those for which tools are available and implementation is required, eg. some helminth and bacterial diseases, and (c) those for which tools are not available and for which drug R & D is limited, the "most neglected diseases", for example, the dengue, leishmaniases and trypanosomiases, have very different requirements.

Three main factors have been responsible for this decade of change: (i) the growth of Public Private Partnerships (more particularly, Product Development Partnerships; PDPs), (ii) the re-engagement of the some parts of the pharmaceutical industry in different models of collaboration, and (iii) a re-focus of academic groups on translational medicine within dedicated centres. For drug development, most changes so far has come through the PDPs, in particular in the Medicines for Malaria Venture, the Drugs for Neglected Diseases initiative the TB Alliance, which manage substantial funding through a portfolio approach to drug development. A substantial amount of the funding, so far, has come from philanthropic organizations, especially the Bill and Melinda Gates Foundation.

The endgame is not just the registration of a new drug but to ensure that the drug becomes an effective treatment, with the need to ensure delivery, compliance, safety tolerability and performance (pharmacovigilance) and access at affordable prices. We Other partnerships have ensured that tools for example ivermectin, albendazole, azithromycin and praziquantel, that have had a major impact on the control and/or elimination of onchocerciasis, lymphatic filariasis, intestinal helminthes, trachoma and schistosomiasis, have become available.

How community-based research into podoconiosis has fuelled policy change in Ethiopia.

Prof Gail Davey

Professor of Global Health Epidemiology, Brighton & Sussex Medical School; Honorary Associate Professor, School of Public Health, Addis Ababa University; Special Lecturer, University of Notting- ham; Founder, Footwork, the International Podoconiosis Initiative.

Over the past ten years, a multidisciplinary program of research into podoconiosis (non-filarial en- demic elephantiasis) has gathered pace in Ethiopia. The program has covered distribution, aetiology (genetic, mineralogical and biochemical), consequences (economic, social and ethical), management of disease (diagnosis, clinical staging, treatment and health systems). To date, over 35 research ar- ticles and 10 reviews and book chapters have arisen from this program, and seven Master theses and four PhD theses have been completed.

In this talk, Prof. Davey will explain how conducting high quality community-based research has had the additional benefit of raising the local and international profile of podoconiosis. The results of advocacy through research have been considerable: inclusion of podoconiosis in the WHO list of Neglected Tropical Diseases, selection of podoconiosis as one of 8 Neglected Tropical Diseases prioritised by the Ethiopian Federal Ministry of Health; and the foundation of the Ethiopian National Podoconiosis Action Network (NaPAN) and a global initative (Footwork, the International Podoco- niosis Initiative - www.podo. org).

Battling schistosomiasis in the Gezira Irrigation Scheme, Sudan

Prof. Mutamad Amin

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This paper analyses changing patterns of infection with S. mansoni and S. haematobium in Gezira Irrigation Scheme, Sudan. Taking a historical perspective, it shows the way in which ecological, biological, social, economic and political issues have shaped patterns of infection, and how differ- ent kinds of strategies have been developed to control schistosomal infection over time. The article provides data using the content analysis method reviewing researches and reports of studies done on schistosomiasis to reveal strategies implemented to impose the control of the spreading of the disease in the area These strategies have been shaped by wider political and economic issues occurring at both national and international levels; and the article shows that this has had a considerable impact on both the prevalence and intensity of schistosomal infection at a local level. By highlighting the inter-play between biological, ecological, social, political and economic issues at local, national and international levels, the article goes on to reflect on the wisdom of prioritizing mass drug adminis- tration for the control of schistosomiasis (at the expense of a more holistic, biosocial approach) in Gezira and elsewhere.

An animal free mycetoma grain model to study the therapeutic efficacy of various antifungal agents against the clinical entity of this infection

Dr. Wendy W.J. van de Sande

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Eumycetoma is a mutilating, chronic, granulomatous, progressive disease of mainly the foot which is most commonly caused by Madurella mycetomatis. Treatment of this infection is difficult and success rates are poor, even although the fungus itself is extremely susceptible towards the azole class of antifungal agents, in vitro. These in vitro results were generated against fungal hyphae, but in vivo, mycetoma causative agents organize themselves in granules called grains. These grains are composed of the causative agent and a protective cement-material. Therefore, in developing a new therapy for mycetoma, the efficacy of the antimicrobial agents needs to be determined against grains. Until now, grains could only be generated in animal models. It is not possible to generate grains in vitro. Several animal models have been developed for mycetoma over the years. These models have been established in different hosts, ranging from mice and guinea pigs to goats and monkeys. But there is a large drawback to these animal models. From our own experience we noted that, already minutes after infection, mice become discomforted. They stay in this miserable state till 3 days after inoculation when they either tend to recover or die. The mortality rate for this infection model is relatively high (20-90% for the high load infections). Therefore there is a need for a model in which grains can be formed without having to use animals. At the moment, the most studied alternative for mammal infection models is the wax moth larvae Galleria mellonella. These larvae have a cellular and humoral immune system and can be maintained at 370C, conditions beneficial for mimicking the attacks mycetoma causative agents will encounter when entering the human host. Furthermore, these larvae have been used as alternative model systems to study the fungal infections candidiasis, aspergillosis and cryptococcosis. For some of these infections, therapeutic efficacy studies have been performed in these models, resembling the therapeutic response found in animal models and in the clinical situation, indicating that Galleria mellonella would indeed be a good model system for the fungal mycetoma infection. In this presentation, I will highlight the development of a M. myceto- matis grain model in larvae of the wax moth Galleria mellonella, the infection itself but also the responses towards commonly used antifungal agents will be shown.

Mapping the Potential Risk of Mycetoma Infection in Sudan

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In 2013, the World Health Organization (WHO) recognized mycetoma as one of the neglected tropical conditions due to the efforts of the Mycetoma Consortium. This same consortium formulated knowledge gaps that require further research. One of these gaps was that few data are available on the epidemiology and transmission cycle of the causative agents. Previous work suggested a soil-borne or

Acacia thorn-prick-mediated origin of mycetoma infections, but no studies have investigated ef- fects of soil type and Acacia geographic distribution on mycetoma case distributions.

Here, we map risk of mycetoma infection across Sudan and South Sudan using Ecological Niche Modeling (ENM). For this study, records of mycetoma cases were obtained from the scientific litera- ture and GIDEON; Acacia records were obtained from the Global Biodiversity Information Facility. We developed ENMs based on digital GIS data layers summarizing soil characteristics, land-surface temperature, and greenness indices to provide a rich picture of environmental variation across Sudan and South Sudan. ENMs were calibrated in known endemic districts and transferred countrywide; model results suggested that risk is greatest in an east-west belt across central Sudan. Visualizing ENMs in environmental dimensions, mycetoma occurs under diverse environmental conditions. We compared niches of mycetoma and Acacia trees, and could not reject the null hypothesis of niche similarity. This study revealed contributions of different environmental factors to mycetoma infec- tion risk, identified suitable environments and regions for transmission, signaled a potential myceto- ma-Acacia association, and provided steps towards a robust risk map for the disease.

Quality control and standardization in flow cytometry – requirements of GLP, GMP, ISO, and clinical studies

Prof. Ulrich Sack

Institute of Clinical Immunology, Medical Faculty at the University of Leipzig, Germany

Flow cytometric methods are well established in patients' diagnostics, process control, and even preparation of cellular therapeutics. Every of these topics are subject to regulatory systems that are as far as possible harmonized in the European community. By growing implementation of ISO 15189 based standardization in European laboratory diagnostics, flow cytometric labs are more and more challenged to introduce compliant quality management systems. Although in most countries accredi- tation of such laboratories is not yet compulsory, proof of following these rules is widely requested. In contrast, implementation of such systems in preclinical and clinical studies is well established; quality control in transfusion medicine and ATMP manufacturing is daily practice. In general, adher- ence to quality management systems is considered to be very hard for cytometry. Therefore, we ana- lyzed consequences of accreditation process for cytometric labs and investigated flow cytometrists' attitudes and misgivings according these requirements. As major challenges, staff qualification, ad- aptation of multicolor antibody panels, and quality assessment has been identified.

Mycetoma a Neglected Medical & Socio-Economic Dilemma.

Prof. Ahmed Hassan Fahal

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Mycetoma is a common health problem, endemic in many tropical and subtropical regions characterised by devastating deformities, disability and high morbidity. It has serious negative so- cio-economic impacts on patients, families, communities and health authorities. Yet, it enjoys mea- gre attention across the globe and that culminated in massive knowledge gaps in various aspects of mycetoma.

To date, its true incidence, prevalence and route of infection are not well characterised, likewise, its susceptibility, resistance and response to medical treatment. This has been badly reflected on the available treatment modalities which proved to be ineffective, have serious side effects and are ex- pensive for patients and health authorities in endemic areas. It is still challenging and hard to treat patients with mycetoma, for which the available antifungal therapy is still not optimal. In order to treat this infection both extensive and destructive surgery and prolonged antifungal treatment are necessary. The treatment outcome is disappointing, characterized by low cure rate and high amputa- tion, high patients follow up dropout and high recurrence rates.

Most of the available mycetoma diagnostic tests are expensive and not available in mycetoma endemic regions and patients need to travel to provincial hospitals for that.

There is no control or prevention programmes or measurements for mycetoma are available world- wide and hence there is need to develop such programmes and measurements.

Diagnosis of Immunodeficiencies

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Innate and chronic immunodeficiencies represent a group of heterogeneous dysfunctions of the im- mune system resulting in impaired defense on infections and tumors. Genetically determined disor- ders of the protective immune function, commonly referred as Primary Immuno Deficiency diseases (PID), and it have been recognised clinically already 60 years ago with the identification of X-linked agammaglobulinemia. Today, the group of PID involves over 280 distinct entities which are scattered to present as phagocytic disorders, complement deficiencies, T-cell deficiencies and – predominantly - antibody disorders. PID are not rare diseases; with a summarised prevalence ranging from 1 in 250 to 1 in 500. However, they are misdiagnosed in many cases because of their subtle clinical image and their prolonged course of disease, which often worsens the outcome. Although increasingly becom- ing appreciated as a major health problem, there is a lack of diagnostic procedures and sophisticated therapeutic perspectives that would allows upon earliest possible diagnosis and a satisfactory treat- ment of patients with primary immunodeficiency diseases.

Primary and acquired immunodeficiencies strongly influence prognosis and outcome of patients. The targeted identification of such patients represents a diagnostic challenge. Diagnostic strategies depend on the clinical presentation, patients' history, and age. Clinical manifestation of primary immunodeficiencies can start in early childhood but also in adults, based on severity and modifying conditions. Frequently, PID are characterised by hypogammaglobulinemia of the IgG, IgM, and/or IgA isotype, respectively, and a resulting clinical presentation consisting of recurrent and chronic infections, particularly of the respiratory, intestinal and genitourinary systems. Awareness of possibly underlying immunodeficiencies and targeted diagnostics is crucial for early diagnosis and therapy.

In children, majority of most severe immunodeficiencies can be detected by new born screening tests carry out with dried blood spot samples (DBSS). Serious impairment of the immune response due to inborn errors of T- or B-lymphocyte differentiation results in immunodeficiency syndromes such as Severe Combined Immunodeficiency (SCID) or Agammaglobulinemia (XLA, ARA). The fatal outcome of these syndromes – if undiscovered and untreated within the first year of life - and the availability of well-established treatment options justify a general newborn screening program for those severe immunodeficiency diseases.

Lymphocytes can be diagnosed efficiently by flow cytometry in adults and in children suspicious on immunodeficiencies. Immunophenoptyping allows differentiation and functional description of immune cells, including lymphocytes, dendritic cells, monocytes, and polymorphnuclear cells. This is of particular relevance in diagnosis of immunodeficiencies, but also in autoinflammatory, auto- immune, and allergic diseases. For differential diagnosis, functional assays with lymphocytes and phagocytes are essential and can be done in a simple and reproducible way.

Currently, the rationale behind the treatment of antibody deficiency diseases is to restore physiological levels of serum immunoglobulins by intravenous or subcutaneous substitution, which has been shown to prevent or alleviate infectious episodes. Cellular and combined immunodeficiencies are eligible to stem cell transplantation.

Contemporary Management of Oral Cancer & Research Perspectives

Mr. Khalid Abdel-Galil

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Squamous cell carcinoma of the head and neck is the sixth most common cancer worldwide. The main risk factors for cancers of the oral cavity, larynx, oropharynx, and hypopharynx are alcohol and tobacco use. In addition, the human papillomavirus is an established cause of oropharyngeal cancer. An experienced multidisciplinary team is necessary for adequate management and optimal outcome. Although single modality therapy is the preferred approach to treatment, locally advanced disease generally requires various combinations of surgery, radiotherapy, and systemic therapy.

This presentation will provide a holistic overview of oral cancer management from presentation to surgery/non-surgical treatments, including some research perspectives and current technological advances assisting management of this disease. It will look at targeted therapies, genomics and molecular advances and future direc- tions, including non-surgical treatments of Head & Neck Cancer. Individualised care provided in a multidisciplinary setting will be discussed.

Drugs for Neglected Diseases initiative (DNDi), a not for profit Research & Development Organization with a strong implication in Sudan.

Dr. Nathalie Strub Wourgaft

Drugs for Neglected Diseases initiative (Geneva)

Drugs for Neglected Diseases initiative is a not for profit organisation founded in 2003 by research institutions from endemic countries affected by neglected diseases and Doctors without Borders with the objective of developing 11 to 13 treatments by 2018. The diseases that were selected are Human African Trypanosomiasis, Chagas Disease, Visceral and Cutaneous Leishmaniasis, Malaria, later onchocerciasis, lymphatic Filariasis and pediatric HIV were included.

Soon after its creation, the Lelishmaniasis East African Platform (LEAP) was set-up, bringing clini- cal experts, academic institutions, Ministries of Health representatives, NGOs, from Ethiopia, Ke- nya, Uganda and Sudan with the objective of promoting and conducting clinical trials for the devel- opment of new treatment options for patients suffereing from leishmaniasis. Since then DNDi has conducted several important studies in the Gedaref State together with the University of Khartoum, the Federal Ministry of Health as well as MSF.

In 2010, based on the results of the first landmark trial, the combination of SSG and Paromomycin was adopted by the WHO experts as 1st line treatment for East Africa and also added to the treatment guidelines in Sudan. Following this, the Ministry of Health in Sudan, MSF and DNDi engaged into a large pharmacovigilance study assessing the SSG-PM combination's effectiveness in field conditions. The results of this large study were presented in Bahir Dar in October 2014, confirming the good results of this treatment.

In total, in Sudan, over 2000 patients were randomized into clinical trials whilst another 2000 directly received treatment and not included in the trials.

The development of Professor El Hassan Centre for Tropical Medicine in Dooka was supported. Since 2012, DNDi engaged into advocacy supporting activities to bring more attention to mycetoma

as a public health issue, together with the Mycetoma Research Centre in Khartoum.

Sudan is highly affected by kala-azar as well as other neglected diseases. DNDi will continue to get more involved with Sudan research experts, in Leishmania as well as in other prevalent disease as part of our research program portfolio.

Island Soqotra: a unique source of medicinal plants with anticancer, antimicrobial, antiviral and antiprotozoal potentials.

Dr.Ramzi A. Mothana

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Despite the immense technological advancement in modern medicine, a large proportion of Yemen population, as elsewhere in many other developing countries, still rely on traditional healing prac- tices and medicinal plants for their daily healthcare needs. The vegetation and floral biodiversity of Yemen including the island Soqotra provides Yemeni traditional healers with an impressive pool of 'natural pharmacy' from which plants are selected as remedies, or as ingredients to prepare herbal medicines (phytomedicines) for a plethora of human and veterinary disorders. Soqotra is considered the "jewel" of biodiversity in the Arabian Sea. Surveys have revealed that more than a third of the plant species of Soqotra are found nowhere else. Different localities of Soqotra were visited between 2004 and 2008 and many traditional healers were interviewed. So about 50 plants were collected, extracted with methanol and hot water and evaluated for their in vitro anticancer activity against three human cancer cell lines (A-427, 5637 and MCF-7) and for their antimicrobial activity against Gram-positive and Gram-negative bacteria as well as multiresistant Staphylococcus strains. More- over, the antiviral activity of 25 plants has been assayed in two in vitro viral systems, influenza virus type A/MDCK cells and herpes simplex virus type 1/Vero cells, at non-cytotoxic concentrations. The methanolic extracts of Ballochia atro-virgata, Buxus hildebrandtii, Dendrosicyos socotrana, Dracena cinnabari, Eureiandra balfourii, Hypoestes pubescens, Jatropha unicostata and Punica protopunica Withanina aduensis and Withania riebeckii exhibited the highest toxicity on all tumor cell lines with IC50 values ranging between 0.29 and 8.2 µg/ml.

The greatest antimicrobial activity was found by the methanolic extracts of Boswellia ameero, Bo- swellia dioscorides, Boswellia elongata, Boswellia socotrana, Buxus hildebrandtii, Commiphora ornifolia, Commiphora parvifolia, Euclea divinorum, Euphorbia socotrana, Jatropha unicostata, Ka- lanchoe farinacea, Leucas samhaensis, Leucas virgata, Pulicaria stephanocarpa, Punica protopunica, Rhus thyrsiflora, Teucrium sokotranum, Withania adunensis and Withania riebeckii.

The methanolic extracts of Boswellia ameero, Boswellia elongata, Buxus hildebrandtii, Cissus hama- derohensis, Cleome socotrana, Exacum affine, Jatropha unicostata and Kalanchoe farinacea showed anti-influenza virus type A activity with IC50-values from 12.5 to 0.7 µg/ml. In addition, 15 plants of the 25 investigated exhibited anti-HSV-1 activity.

Input of flow cytometry in the diagnosis of Primary Immune Deficiencies

Prof. Mohamed-Ridha Barbouche

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Over the past three decades, flow cytometry has emerged as an invaluable technology in clinical laboratories and has contributed significantly to investigate the immune system cell components. Its unparalleled ability to simultaneously identify characteristic physical cell properties, cell numbers, cell functions, and numerous cell gene products at rates of thousands of cells per second has resulted in the development of a large repertoire of diagnostic, prognostic, and monitoring assays.

There are currently more than 200 recognized primary immune deficiencies that have been classified and whose underlying genetic defects are known. The diagnosis of many of these PIDs is supported strongly by a wide variety of flow cytometry applications. Abnormalities detected by flow cytometry can be grouped broadly as having (1) relative or absolute decrease in a specific subset or subsets, (2) loss or abnormal expression of a specific cell-associated marker or markers, and (3) loss or abnormal function.

Routine immmunophenotyping for the identification of cell subsets and/or cell markers abnormali- ties in the peripheral blood of patients suspected to suffer primary immunodeficiency diseases along with various routine functional studies helping diagnose these diseases will be discussed, using vari- ous examples from our experience of PIDs amenable to assessment by flow cytometry and classified according to the recent classification of primary immunodeficiencies published by the International Union of Immunological Societies Primary Immunodeficiency experts committee.

Flow cytometry has been and continues to be an invaluable tool for the diagnosis and monitoring of patients suspected of having PID.

At wenty year experience of Primary Immune Deficiencies' investigations in resource-limited settings

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Primary Immune Deficienes (PID) are a heterogeneous group of inherited disorders in which im- mune system dysfunctions cause an enhanced susceptibility to infections that is the common clinical feature of these diseases. To date, more than 200 genes have been identified and associated with as many different immunodeficiencies. The frequency of PIDs is higher in North-Africa and Middle- East as compared to Europe and North-America. Indeed, our population is characterized by a high frequency of consanguineous marriages which may reach 50% in rural areas. This may account for the higher incidence of autosomal recessive immunodeficiencies observed.

During the last twenty years, we've diagnosed and investigated at the Institut Pasteur de Tunis, a resource-limited institution, 655 tunisian cases of PIDs including patients with combined immuno-deficiencies, antibody deficiencies, phagocytosis defects, complement deficiencies and other well-defined immunodeficiencies.

Our series is characterized by a high incidence of autosomal recessive diseases including Ataxia-

telangiectasia, Bare Lymphocyte Syndrome, Mendelien Susceptibility to Mycobacterial Disease and Leukocyte Adhesion Deficiency. Moreover, we've observed a high frequency of autosomal recessive forms of classically X-linked immunodeficiencies such as Severe Combined Immunodeficiencies, Agammaglobulinemia, HyperIgM Syndrome and Chronic Granulomatous Disease. The immuno- genetic investigations and the establishment of an accurate diagnosis allowed an appropiate and targeted treatment of the affected children e.g. bone marrow transplantation, substitutive intravenous immunoglobulins, IFNg or GM-CSF therapy. This did also allow us establish a preventive approach by genetic counseling and prenatal diagnosis. Moreover, we did contribute to dissection of the IF- Ng-IL12/23 dependant pathway in patients with mendelian susceptibility to mycobacterial diseases, which might be a model to better understand immune responses during tuberculosis. We did also con- tribute to the World Health Organization efforts to eradicate poliomyelitis by studying PIDs patients who can be directly or indirectly infected by oral vaccine strains and may become chronic excretors of polioviruses. This is a major concern since long-lasting strains in the intestine of these patients have been shown to be able to revert and cause vaccine-derived poliomyelitis outbreaks, representing a potential reservoir for infection in the post eradication era. Furthermore, we contributed to better understand the role of TH17 cells in susceptibility to severe fungal diseases and we discovered, re- cently, a novel gene underlying susceptibility to staphylococcal infection, inflammation and allergy in hyper-IgE syndrome patients.

In conclusion, the study of these diseases helps establishing accurate diagnosis and appropriate treat- ment of patients. It also contributes unraveling specific immunological pathways, in our settings rare autosomal forms offer a privileged physiopathological model for infections including some which are linked to global health challenges.

Immune escape of Cancer Cells

Prof. Michael Kirschfink

Institute of Immunology, University of Heidelberg, Germany

Effective antitumor immune response depends on the interaction between several components of the immune system, including antigen-presenting cells, antibodies, complement and different T cell subsets. Cancer cells have developed multiple strategies to modulate our immune system for evasion. Recent advances in cancer immunology allow for a better understanding of the mechanisms tumors use to execute immune escape and of the relationship the tumor establishes with immune cells. Many cellular and molecular events reflect that the tumor undergoes a continuous remodeling at the ge- netic, epigenetic and metabolic level to acquire resistance to cell killing mechanisms by complement and apoptosis. Malignant cells effectively employ literally all the components of the host's immune system to escape from their antitumor effects.This includes the accumulation of suppressive cells like Treg and myeloid derived suppressor cells as well as the release of inhibitory factors into the microenvironment.

Furthermore, tumor-propagating cells must also escape from immune-mediated destruction. The ability to persist and to initiate neoplastic growth in the presence of immunosurveillance is decisive for the survival of cancer stem cells. After a general overview this presentation will exemplarily provide a deeper insight into strategies how cancer cells escape immune recognition and how these mechanisms can be neutralized with potential impact on tumor immunotherapy.

Complement deficiencies: Clinical impact and diagnostic strategies

Prof. Michael Kirschfink

Institute of Immunology, University of Heidelberg, Germany

Complement as a major component of the innate immune system has a crucial role in the protection against infections. By orchestrating the immune response, complement substantially contributes to homeostasis. However, complement may turn against healthy tissue with severe consequences if not properly controlled. Complement deficiency cases comprise about 5 to 10% of all primary immunodeficiencies. As "experiments of nature" they have significantly contributed indefining the role of complement in host defence. There is great variation in the spectrum of disorders associated with complement deficiency dependent on which complement protein and activation pathway is affected. Genetic deficiency of any early component of the classical pathway (C1q, C1r/s, C2, C4) is often associated with autoimmune diseases, especaly with SLE due to the failure of clearance of immune- complexes and apoptotic materials and impairment of normal humoral response. Individuals, defi- cient of properdin and of the terminal pathways (C5 to C9) are highly susceptible to meningococcal disease, indicating that its cytolytic property is of particular importance in the host defense against Neisseriae. Deficiency of C1 Inhibitor, either inherited (hereditary angioedema, HAE) or acquired, results in episodic angioedema. Mutations affecting the regulators factor H, factor I, or CD46 and of C3 and factor B leading to severe dysregulation of the alternative pathway have been associated with renal disorders, such as atypical hemolytic uremic syndrome (aHUS) and less frequent with membranoproliferative glomerulonephritis (MPGN).

The diagnostic approach leading to the identification of a complement deficiency involves a multi- step process that starts with functional screening of each activation pathway and proceeds in special- ized laboratories with the characterization of the defect at functional, protein and molecular level. Careful handling and storage of blood samples is of critical importance for meaningful complement analysis. Leading international diagnostic complement laboratories have assembled for quality as- surance and further development of analytical tools.

Tropical Medicine in 2015

Prof. Ed E Zijlstra

Rotterdam Centre for Tropical Medicine, the Netherlands, Consultant for DNDi in Leishmaniasis.

Tropical Medicine has changed over the years. It dates back to the middle of the 18th century and it became a formal discipline in 1900. While initially it was best described as colonial medicine aimed to protect the interests of the British Empire, later the focus shifted to include all health problems of those living in tropical areas. Tropical schools were established e.g. in London, Liverpool, Hamburg and Antwerp that taught tropical medicine as a formal discipline, that carried out research and that worked with international organizations such as the World Health Organization (WHO). Over the years more attention was given to prevention and control that is often mentioned in the context of International Health.

In the 20th and 21st century, emergency aid in tropical areas (as provided by Médecins sans Frontières), emerging infectious diseases (e.g. dengue, SARS, MERS), HIV/AIDS, travel medicine and neglected tropical diseases were all added to the spectrum of Tropical Medicine. While recently the

Ebola outbreak re-emphasized the original image of Tropical Medicine as a discipline dealing with exotic infections, the non-communicable diseases (NCDs) are now deservedly receiving more attention, illustrating the wide and complex spectrum of this specialty.

Tropical medicine is probably best defined as Medicine (read Surgery, Paediatrics etc.) in the Trop- ics, i.e. how to practice medicine in a tropical area taking into account the local epidemiology, local expertise and often limited resources. Training and research are essential components.

Telemedicine – recent advances

Dr. Victor Patterson

Telemedicine, the practice of medicine when the doctor and the patient are not in the same place, has been shown to be an effective way to deliver services in many different settings. Applied properly it can either enable a service to be provided that could not be done face-to-face (FF) or it can improve the quality of an existing FF service, usually by making it more patient-centred or less expensive. Telemedicine has been used successfully in both rich and poor countries using email, webservers, telephone, texting or videolink. Most telemedicine has been between a specialist and another doctor or health professional but some has been between a specialist and a patient. The latter has become much more possible with the widespread adoption of mobile phones. Also the increased adoption of "smartphones" which are able to access the internet either over a wireless or 3G network has produced a new branch of medicine called "mhealth". Applications (apps) can be written specifically for smartphones and these have a number of functions including enabling non-specialists to diagnose episodes of altered consciousness as epilepsy or not. This has the potential to devolve medical functions safely to non-doctors and this should enable more people with untreated epilepsy to be treated. In richer countries tele-monitoring of patients with chronic conditions such as diabetes, and congestive heart failure is being used increasingly and has been shown to prevent hospital admissions. The adoption of telemedicine in most healthcare systems has been slow because the benefit of telemedi- cine is to patients and not to doctors. Doctors need to be incentivised to use telemedicine for their patients' benefit. How to provide that incentive is challenging and may be a role for governments.

Cerebrovascular Disorders: Small Vessel Diseases of the Brain

Prof. Raj N Kalaria

Institute of Neuroscience, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, United Kingdom

In this lecture, I will focus on the main types of cerebrovascular disease (CBV) that lead to vascular cognitive impairment (VCI), which incorporates all causes of vascular disease. The integrity of the vasculature is essential for the optimal functioning of the brain. In addition to the cardiovascular system, brain vascular control mechanisms are vital for the maintenance of the neurovascular milieu, created by nerve terminals, astrocytic endfeet and the microvasculature. The degree of cerebral grey matter damage, neuronal death and survival will be dictated by the multiplicity, size and laterality of the tissue injury or the extent of vascular disease. Anatomical features of the circulation includ- ing the size of vessels and their distribution as well as vascular wall cellular elements e.g. arterioles versus capillaries are important factors in defining the pathology and causes of CBV such as large infarcts, haemorrhages, lacunes, microinfarcts, amyloid and non-amyloid angiopathies, vasculitis, arterial dissection and aneurysms. The origin and degree of vascular occlusion or injury and whether this results in ischaemic or haemorrhagic lesions are further factors which define the extent and se- verity of damage. Atherothromboembolism attributed to large vessel disease and subcortical lesions (including the white matter) described by intracranial small vessel disease (SVD) are considered to be the main causes of cerebral ischaemia. Sporadic SVDs of the brain account for about 25% of all conditions, which involve transient ischaemic episodes and strokes. SVD is actually a radiological term but entails tissue changes affecting arteries, arterioles, capillaries and small veins. It involves lacunar infarcts and multiple microinfarcts in subcortical structures including the white matter, basal ganglia, thalamus and the brainstem. Among post-stroke survivors who develop dementia, particu- larly vascular dementia (VaD) more than 50% have strong evidence of SVD. Several inherited forms of SVD have been described in the past decade. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common of these caused by

>190 different mutations in the NOTCH3 gene. It is characterised by lacunar infarcts accompanied by diffuse white matter changes and severe arteriosclerosis in the general absence of risk factors for cerebrovascular disease. Recent elucidation of less common hereditary small vessel diseases include CARASIL, RVCL and COL4-related conditions.

Our work is supported by the Medical Research Council (UK), Alzheimer's Research Trust (UK) and Dunhill Medical Trust (UK).

Stem cells in Dental Tissues and Their Regenerative Potential

Dr. Ikhlas Awad Elkarim

Faculty of Dentistry University of Khartoum.

Stem cells provide an attractive novel therapeutic approach for repair and replacement of pathologically damaged tissues. Adult stem cells are becoming largely recognised as potential source of stem cells for future therapy given the controversy around embryonic stem cells. Dental tissues are readily available source of adult stem cells following teeth extraction. Within teeth Stem cells reside in the dental pulp, the periodontal ligament and the apical papilla. These cells are multipotent stem cells of mesenchymal origin that can be successfully differentiated into various specialised cells. Using explants culture and magentic beads separation methods we isolated stem cells form dental pulp and periodontal ligament. We developed a protocol for in-vitro differentiation of dental pulp stem cells into functional neurons and odontobalsts. The osteogenic potential of periodontal ligament stem cells is also explored in addition to the effect of inflammation on renewal and regenerative capacity of these cells. We are particularly interested in the factors that determine fate and terminal differentiation of stem cells to help develop mechanisms for directed differentiation of stem cells for future tissue engineering and regenerative medicine.

Podoconiosis

Prof. Melanie Jane Newport

Brighton and Sussex Medical School and Brighton and Sussex University Hospitals Trust, Brighton

Podoconiosis is a non-infectious geochemical disease that results in swelling of the lower legs. It is caused by long term exposure of bare feet to red clay soil derived from volcanic rock. In southern Ethiopia, where much of our research has been conducted, and north-western Cameroon, it affects

5-8% of the population and is more common than HIV, TB or malaria. Podoconiosis imposes im- mense economic burdens (the estimated cost to Ethiopia's economy is $208 million per year) and severe social stigma. Very little research on disease aetiology or pathogenesis has been done, yet such research is needed for rational deployment of limited resources towards prevention, treatment and ultimately eradication of the disease. There is convincing evidence that an area of the genome com- monly involved in human responses to infectious and environmental challenges plays a major role in susceptibility to podoconiosis. In this talk I will discuss the work we have undertaken to identify the genetic variation that predisposes to podoconiosis and how this work could have impact on the lives of people affected by the condition. For example, establishing the importance of genetic susceptibil- ity has justified the use of a family history tool in determining which children should be offered shoes for prevention of disease, when shoes are a scarce resource.

Neglected Tropical Diseases – a case for eradication and the related public health challenges

Prof. Marcel Tanner

Swiss Tropical & Public Health Institute, University of Basel, Basel, Switzerland

The global health community pays renewed attention to evaluating the feasibility of elimination and eradication of additional communicable diseases, particularly Neglected Tropical Diseases (NTDs) besides continuing to aim at reducing the burden of ill-health. While the health and economic ben- efits of disease elimination and subsequent eradication may be substantial, elimination initiatives represent resource-intensive efforts with associated opportunity costs. Thus, besides studying the biomedical approaches and the accompanying R&D agenda, any attempt of considering elimination and eradication efforts also entail engaging into developing the Eradication Investment Case (EIC). An EIC is an economic assessment addressing all three fundamental economics questions: 1) the "What question", that compares remaining in control mode versus moving towards elimination and then eradication; 2) the "How question", that assesses which intervention/s or strategy/ies should be adopted by which stakeholder, how much resources would be required and how they could be mobilized; and 3) the "For whom" question, that assesses who would benefit from control or elimination in terms of health and economic benefits, and the likely impact on equity and fairness.

We will presents the rationale, the approaches to be pursued and the main methodological challenges of developing EICs for NTDs and will show that the EIC approach goes beyond traditional efficacy and efficiency measures to take into account multiple dimensions. An EICs will not only test the applicability and feasibility of elimination/eradication but will also serve to inform decisions of global and national policy makers.

At the level of public health action, a key towards success is the development of surveillance and response approaches that are required to effectively achieve NTD elimination / eradication in a given endemic setting. Introducing surveillance-response approaches represents a paradigm shift from maintaining comprehensive monitoring and evaluation activities to focusing on the approaches that rapidly detect remaining / reemerging pockets or "hot spots" of transmission and allow swift public health action with well-tailored integrated response packages to interrupt transmission of NTDs. The main feature of the surveillance response systems / approaches is that they are based on the concept of collecting minimal essential data in space and time to identify pockets of transmission or reintroduction within the context of a given health and social system.

EICs and the introduction of surveillance-response systems integrated into the respective national health system will form the crucial cornerstone for any effective and integrated use of old and new control/elimination tools/approaches and, thus, for any successful NTD elimination/eradication program.

Globalization and Medical Education

Yousif Eltayeb

Consultant Surgeon, Rashid Hospital, Dubai Surgery Residency Program Director, Professor of Surgery, Dubai Medical College

Globalization has become an inevitable fact that touched all aspects of life. The phenomenon has affected education at large including medical education. With knowledge, technology, quality and cost effectiveness becoming trademarks of the 21st century social transformation has escalated. The impact of that transformation has resulted in a change of patient relationship with patients chang- ing into customers and treating doctors into health care providers. Those customers are no longer interested in just treatment but in a high quality cost effective treatment. The consequence of that mandates a change in the process of medical education and training process to cope with the use of high tech being currently in use.

Looking at the above facts and the prevailing situation of economic hardships and the state of medi- cal service in developing countries the magnitude of the problem could be appreciated. The problem is escalated by the fact that the chances of training in advanced countries are becoming extremely scarce depriving overseas candidates from getting advanced training to disseminate when they return back home.

To solve that problem developing countries have to find a solution by first improving health service system, improve undergraduate curricula and the quality of local training programs to a level internationally credible if they intend to survive the impact of globalization. That will not be possible without improving health systems and infrastructures, acquiring a culture and environment for education and professional development, and investing in research and technology.

Aspects of Stem cells and Epithelial Mesenchymal Transition in the diagnosis and biological behavior of selected tumors in Sudan

A M EL Hassan

Institute of Endemic Diseases, University of Khartoum and EL Hassan Center for Histopathology Services

As pathologists we use immunohistochemistry to identify certain markers that help us to decide if the tissue is normal, hyperplastic or neoplastic. If neoplastic is it benign or malignant? If malignant what is the degree of differentiation and whether it is likely to metastasize or not?

In this presentation I discuss the importance of molecular biology for the pathologist engaged in rendering histopathology services and performing research. In particular, the presentation addresses cancer and its differential diagnosis using modern immunohistochemical technology. I looked for some gene products that help in confirming a cancer, its type, degree of differentiation and whether it is expressing genes that are associated with a metastasizing potential. The other important area to be discussed is the phenomenon of Epithelial Mesenchymal Transition (EMT) in which the tumor has both epithelial as well as mesenchymal tissue even in the H&E stained routine sections. The reverse of this is Mesenchymal Epithelial Transition (MET). This will also be bewildering to the practicing pathologist and he needs to use immunohistochemical markers for certain genes in order to make the proper diagnosis. The gene

products I looked for are CD44, OCT4, P63 and Cadherins. As examples we tested esophageal squamous cell carcinomas with different degrees of differentiation and a rare carcinoma variant known as basaloid squamous cell carcinoma. We showed for the first time that the squamous and basaloid components are of different histogenesis. Details will be given in the presentation

Epithelial mesenchymal transition and mesenchymal epithelial transition and their significance in the biology of tumours will be presented. We used EMA, Cytokeratin 20, Vimentin, S-100 protein, CD

44, E-Cadherin to study the tumours.

Bartonella infection: An emerging neglected disease in Sudan

A M EL Hassan, Waleed Elamin and Lamyaa EL Hassan

IEND and EL Hassan Center for histopathology, Khartoum

Bartonella infection occurs in three forms: Cat scratch disease (CSD) due to Bartonella henselae, Trench fever due to Bartonella Quintana and Carrión's disease caused by Bartonella bacilliformis. In this presentation we describe CSD for the first time in Sudan. CSD occurs worldwide and may be present wherever cats are found. The bacteria infect the red cells of cats which are usually symptomless. ransmission of the bacteria between cats is by fleas. Transmission to humans is by cat bites and scratches. Of the thirty cases we had in 2013 and 2014 the sites affected included the skin, subcutaneous tissue, lymph nodes, the lung, the spleen, Brain, spinal cord, bone, breast, and retroperitoneum. The Bartonella we found was identified as B henselae by a specific monoclonal antibody. The report is from a single center in Khartoum. The condition is perhaps more common than is believed

In old old article published in Acta Tropica 1969 a single case from Sennar was diagnosed as possibly Bartonella quintana. At that time specific antibodies against B henselae were not available. From the clinical data and stained morphology it was most likely Bartonella henselae At that time monoclonal antibodies and PCR were not available. From the description I think it was B henselae

Tuberculosis: basics, burden, impact, challenges, innovations, Integration a Human Rights based perspective to TB Control & the post-2015 Strategy.

Asma I, ElSony & Hanaa A.ElSadig

The Epidemiological Laboratory, Khartoum, Sudan

Government commitment, diagnosis through microscopy, standardized and supervised treatment, uninterrupted drug supply, and regular monitoring, which together constitute DOTS— a strategy which was developed by the International Union Against Tuberculosis and Lung Diseases and supported by the & recommended by the WHO as a tuberculosis control strategy—remains essential for controlling tuberculosis. DOTS have helped make remarkable progress in global control of the disease over the past decade. The gain is evident: nearly 21 million patients have been cured of tu- berculosis. However, global statistics suggest that DOTS alone is not sufficient to achieve the 2015 tuberculosis-related Millennium Development Goals (MDG) and the Stop TB Partnership targets.

Two other 2015 global targets for reductions in

disease burden (prevalence and mortality rates) and two additional indicators fit within the MDG framework. In addition, 2015 targets for the response needed to address the specific challenges of multidrug-resistant TB (MDR-TB) and the TB/ HIV co- epidemic were set within the Global Plan to Stop TB 2011–2015.

Tuberculosis, a disease of poverty, is a measurable indicator of equitable development Inclusion of TB in the MDGs has contributed to making progress in global TB control Union/WHO TB strategy has helped cure 51 million patients and save 20 million lives 2015 MDG target of halting and begin- ning to reverse TB incidence has been achieved.

Compared to 1990, TB mortality has been reduced by 41% and will be halved in 2015 R&D is now finally resulting in new tools and scientific breakthroughs. However, TB incidence decline is too slow to realize the vision of a TB free world. Every year, still 1.4 million people die of TB and 8.7 million suffer from.

However, TB incidence decline is too slow to realize the vision of a TB free world Every year, still

1.4 million people die of TB and 8.7 million suffer from it

Ambitious targets and expanded efforts required post-2015 to accelerate progress: Goal: "Zero TB deaths" besides "TB elimination as a public health problem" Target 2025: "Halve TB mortality and prevalence rates compared with 2015"

Limb-girdle muscular dystrophy (LGMD): Diagnosis in an Arab country

Riadh Gouider, Imen Kacem

Department of Neurology, Razi Hospital. Tunis -Tunisia

Limb-girdle Muscular Dystrophies (LGMD) are heterogeneous inherited muscle disorders characterized by progressive weakness and muscle wasting. They show a wide spectrum of clinical courses, varying from very mild to severe. It is a genetically heterogeneous group of diseases with dominant (LGMD1) and recessive (LGMD2) inheritance. To date, at least 31 loci have been identified. The different subtypes can be distinguished by immunohistochemical analysis in a muscle biopsy speci- men in order to guide and abbreviate the molecular genetic investigations. There is a geographical difference in their incidence.

LGMD2 are prevalent in Arabic countries because of the high rates of consanguinity. Many genes were identified in these countries, especially in Maghreb. LGMD type 2C, or δ-sarcoglycanopathy, is the most frequent in North African populations as a result of the founder c.525delT mutation in the Sarcoglycan gene. It was firstly described in Tunisia, in 1977, by Ben Hmida in a large consanguine- ous Tunisian family with Duchenne like phenotype affecting both girls and boys. It is characterized by a childhood onset of progressive muscular dystrophy. The mean age of onset is between 5 and 6 years, and half of these patients lose ambulation by age 12 years. Calf hypertrophy and lumbar lordosis are common. Diagnosis confirmation is based on muscle biopsy and molecular study. The scarcities of specialized centers and difficulties that can prevent patients from benefitting from im- munohistochemical analysis complicate their diagnosis, management, and genetic counseling. We therefore propose, in our context, that screening for c.525delT could be the first test for AR-LGMD, with a good cost/ benefit ratio in public health strategies, until access to immunohistochemical analy- sis will be generalized. This might be useful not only for management of patients, genetic counseling, and prenatal diagnosis in families but also for novel therapeutic approaches and future clinical trials.

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The Vancouver Style of Reference Formatting

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- The justification of an internationally accepted style of reference citation can be summarized as follows:-
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- To successfully secure research funding, the research proposal including the existing literature on which it is based should be convincing and easily accessed by reviewers.
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e.g. Rose ME, Huerbin MB, Melick J, JK et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res 2002; 935: 40-6.

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Author(s) of a book

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Elmunshid HA. Special senses. In: Sukkar MY, Elmunshid HA, Ardawi MS, editors. Concise Human Physiology 2nd Edn. Oxford: Blackwell Science; 2000.p.401-23.

Reference on-line

Example (from The Michener Institute for Applied Health Sciences, Learning Resource Centre: Irc@ michenere.ca).

Book on the Internet

Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/o309074029/html/.

Internet homepage/website

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org.

For a fuller range of examples of citation from other sources of references, there are innumerable sites on the internet. Please also consult the publications cited in KMJ instructions to authors and the references cited below:-

1. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication [home-page on the Internet]. Philadelphia, PA: International Committee of Medical Journal Editors; [updated 2003 Nov; cited 2004 Oct 9]. Available from: http://www.icmje.org/.
2. Style manual for authors, editors and printers. 6th Ed. Milton, Qld: John Wiley & Sons; 2002.