MEETING REPORT

Diagnostics in infections*

The theme of the 11th Sir Dorabji Tata symposium was 'Diagnostics in Infections'. The symposium coincided with the completion of 76 years of the establishment of the Dorabji Tata Trust, a twin institute of the Indian Institute of Science (IISc), Bangalore. P. Balaram (Director, IISc), while presiding over the inauguration, mentioned that the symposium has been held every year in the past decade with differing themes. The 10th symposium held in March 2009 coincided with the centenary of IISc. D. Raghunath (Sir Dorabji Tata Centre for Research in Tropical Diseases, Bangalore) talked about the advantages of nucleic acid-based methods in early diagnosis of diseases and their role in revolutionizing the field of medicine.

India has a profound history of infectious diseases such as leprosy and tuberculosis, which require immediate attention. V. M. Katoch (Indian Council of Medical Research, New Delhi) suggested that the tools to detect a disease can be based more on the symptoms; this is presently lacking in India. Peripheral areas of the country need to be acquainted with health centres to prevent more people from travelling to distant places for treatment. For detection of viral diseases, which are more rampant, molecular techniques must be made available at all the medical centres.

Jagadish M. Deshpande (Enterovirus Research Centre, Mumbai) spoke about the Global Polio Eradication Initiative that adopted the strategies of high Oral Polio Vaccine coverage through routine immunization, Acute Flacid Paralysis surveillance with virology laboratory support, supplementary immunization, mopping-up immunization, preparedness to stop imported/re-introduced virus, minimizing risk of accidental/intentional spread of the virus in post-eradication years, and cessation of polio vaccination.

A new intratypic differentiation algorithm for poliovirus was developed and fully implemented in the Global Polio Laboratory Network (GPLN) by 2007. Previously it took 106 days to mount a field response; with the new algorithm, all activities could be completed in 68 days. Future diagnostics in GPLN would incorporate the replacement of enzyme-linked immunosorbent assay (ELISA) by molecular methods and direct detection of poliovirus in stool samples.

Leprosy, lymphatic filariasis (elephantiasis), onchocerciasis (river blindness), schistosomiasis, soil-transmitted helminths (intestinal parasites) and trachoma are some of the neglected tropical diseases prevalent mostly in developing countries. Infections caused by parasitic helminths account for 8 out of the 13 major neglected tropical diseases. New approaches to the diagnosis of these infections were presented by Thomas B. Nutman (National Institutes of Health, USA). Sensitivity, specificity, positive predictive value and negative predictive value are the general concepts used in assessment and diagnostics. Nutman discussed the examples of *Loa loa*, *Strongyloides stercoralis* and *Wuchereria bancrofti*.

Soumya Swaminathan (World Health Organization, Geneva) touched upon the neglected tropical diseases affecting neglected populations and proposed approaches such as the Global Health Accelerator, Innovation Fund, Priority Review Voucher, Advance Market Commitment and Patent Pool. Future diagnostics would rope in ultrasensitive acoustic sensors to detect viruses, bacteria and proteins in unprocessed blood, high sensitivity detection calls to allow less invasive disease diagnostics and the 'electronic nose' concept. Chandrasekhar Nair (Bigtec Labs, Bangalore) gave an example of micro electromechanical systems (MEMS)-based biosensors which provide higher sensitivity and specificity, data reliability, faster results and better interpretation. The challenges in BioMEMS-based diagnostics are: access to high-end fabrication facilities, fabrication competency building, awareness, training and education.

After introducing the background information on mass spectrometry and the epidemiology of a flu virus, Utpal Tatu (IISc) highlighted the role of mass spectrometry (MS) in the detection of flu protein. MS is now known to be used for quick identification of proteins and to sequence proteins in an effective manner. A high-resolution MS can be used for sub-typing influenza virus from clinical samples and serves as a diagnostic tool. Because the strain is fast evolving, this would serve as a better and more sensitive diagnostic tool than the existing methods.

Neeru Singh (Regional Medical Research Centre for Tribals, Jabalpur) pointed out that 2.4 million malaria cases per year are reported from South Asia, of which 75% is from India; 65% of these is from six states including Madhya Pradesh (MP). A study was done in Shivpuri and Dindori districts of MP comparing the performance of five commercially available rapid diagnostic tests (RDTs) versus polymerase chain reaction (PCR) and microscopy, for diagnosis of *Plasmodium falciparum* and *Plasmodium vivax*. Among the five RDTs, the First Response Malaria combo test was the most sensitive, even though less specific, for *P. falciparum*. The test was moderately sensitive and specific for *P. vivax*. Only microscopy and RDTs are viable options at the present time.

Asish K. Mukhopadhyay (National Institute of Cholera and Enteric Diseases, Kolkata) traced the developmental history of test methods for cholera, including the hanging drop method (1885) and Bandi's tube method (1910). In 2003, researchers at the Institute Pasteur, France, developed an immunochromatographic dipstick test which involves minimum technical skill, simple assay and can be read in ~10 min. This technology has been transferred to Span Diagnostics Limited, India and is now commercially produced as 'Crystal VC'.

Different aspects of tuberculosis diagnostics were dealt with by Camilla Rodrigues (P. D. Hinduja National Hospital and Medical Research Centre,

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Mumbai), Jaya S. Tyagi (All India Institute for Medical Sciences, New Delhi) and V. Kumaraswami (Tuberculosis Research Centre, Chennai). Kumaraswamy highlighted the burden of tuberculosis, which is high in India, and diagnosis for its control. Rodrigues explained the three techniques used in diagnosis of the active disease – microscopy, culture and species identification, and molecular techniques. Accurate identification is essential because there are 125 strains of *Mycobacterium*. Sputum microscopy is a rapid and inexpensive technique, but has some disadvantages such as poor sensitivity in HIV-positive patients and limited value in children. Tyagi presented her work on improving the sensitivity of microscopy. She said that naked DNA present in the supernatants of freshly isolated samples, which is discarded otherwise, could also be used for diagnosis.

Savitri Sharma (L. V. Prasad Eye Institute, Bhubaneswar) focused on the bacterial and fungal infections of the eye in her talk. She mentioned that all parts of the eye are susceptible to infections, but infections commonly occur in the external ocular surface and in the inner eye. Bacteria may enter the eye orbit from the throat. Infection results from a break in the epithelium caused by trauma or by wearing contact lenses. She concluded that PCR is the best method to detect the infections. Lily Theres (Sankara Nethralaya, Chennai) gave an overview of the molecular diagnostics in infectious diseases of the eye. Conventional methods of detection of ocular infections are time-consuming and have low sensitivity. Therefore, a more sensitive nucleic acid-based technique is required, an example of which is PCR.

R. B. Kotabagi (Armed Forces Medical College, Pune) spoke on molecular techniques in microbial forensics. A databank of signature markers of microorganisms that can be used as biological weapons is necessary. Molecular and non-molecular methods are available for 'sign markers'. Single nucleotide polymorphism analysis by real time-PCR is the only method for degraded/small-quantity samples (amplicon length 60–80 bp). Complete genome sequencing is the best choice for mutations. The limitations in molecular techniques comprise: (a) difficulty in interpretation; (b) ecological factors like effects of antibiotics and laboratory culture conditions may bring about variations; (c) population factors like clonal (asexual) inheritance have to be taken into account. A multidisciplinary approach using both molecular and non-molecular methods is needed.

B. V. Ravi Kumar (XCyton Diagnostics Limited, Bangalore) highlighted the advantages of the XCyton Syndrome Evaluation System in the diagnosis of critical infections. This is a paradigm shift from disease-based diagnostics where there is a sequential search for one organism after another (*A*, *B*, *C*. . .till you get '*N*') to simultaneously looking for all pathogens that could probably cause a disease (*A*, *B*, *C*. . .*N* are all tested).

The clinical determinants of HIV infection, the CD4 T-cell count and virus load, do not enable correct timing for commencement of treatment for patients. There is a need to identify host cell factors that regulate T-cell function and/or virus replication in CD4 T-cells. Annapurna Vyakarnam (King's College London, London) described the worldwide progress in understanding HIV pathogenesis and a novel marker of HIV disease progression (WFDC1/ps20) identified in her laboratory.

Saumitra Das (IISc, Bangalore) noted that vaccines are currently available only for Hepatitis A and Hepatitis B; the Hepatitis B virus (HBV) vaccine can be used for Hepatitis D virus infection. Efforts have been made to identify virus-specific targets for inhibition of viral proliferation in the three areas of adsorption, internalization and particular virus function. Novel strategies include the ribozyme technology in which therapeutic ribozymes are capable of catalytic cleavage of target viral RNAs. Das' research group has been working on Hepatitis C virus (HCV), particularly on a synthetic peptide LaR2C, which inhibits HCV replication in the liver. They have also demonstrated successful delivery of antiviral RNAs into mouse liver using *Sendaivirus*-based virosome system and subsequent inhibition of HCV translation in the whole animal.

V. Ravi (National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore) discussed the viral diagnostics status in India. The Indian industry has developed rapid diagnostics for HIV, HBV and HCV. The JEV IgM capture ELISA kit was developed at NIMHANS for detecting Japanese encephalitis. Some (available) diagnostic assays include the JEV TaqMan® RT–PCR assay and LAMP (reverse transcription loop-mediated isothermal amplification assay). Future diagnostics include the AES chip for outbreaks and AES chip for immunocompromized developed at NIMHANS.

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