Meeting report: A celebration of the work of Professor Tony Hart, Liverpool, United Kingdom, 7 March 2009

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Over 300 delegates participated in this scientific meeting to celebrate the career of the late Professor Tony Hart, who was Head of Department of Medical Microbiology, University of Liverpool, from 1986 until his death in September 2007. The meeting, which was opened by Professor James Stewart (Head, School of Infection and Host Defence, University of Liverpool) and closed by Professor Bernard Brabin (Head of the Child Health Group, Liverpool School of Tropical Medicine), captured some of the major elements that distinguished Tony Hart’s remarkable career. These included: broad research interests spanning both human and veterinary medicine; the ability to conduct both clinical and basic science research with equal skill and vigour; and his phenomenal mentorship of postgraduate students. Each session was chaired by a colleague who had co-supervised students with Tony Hart and 10 former students spoke about the work that they undertook under his supervision. Session themes included herpes viruses (cytomegalovirus and herpes simplex virus), paediatric infections (respiratory syncytial virus, rotavirus, Neisseria meningitidis and Salmonella typhi) and zoonoses (non-typhoidal salmonellae, Cryptosporidium, antibiotic resistance and emerging infections), reflecting the broad range of Tony Hart’s contribution to medical microbiology.

Keywords: paediatric, tropical, zoonoses, students

Introduction and welcome

The conference was opened and the participants, who included family, friends and colleagues of Tony Hart, were welcomed by Professor James Stewart, Head of the School of Infection and Host Defence, University of Liverpool. Professor Stewart said that Tony Hart was a great collaborator and that a major achievement he will be remembered for is the number of networks of research groups he initiated not only at Liverpool but around the world. Major initiatives included the National Centre for Zoonosis Research (NCZR) at the University of Liverpool that he co-founded with Professor Malcolm Bennett, the National Institute for Health Research Biomedical Research Centre in Microbial Diseases in Liverpool that he jointly established with Professor Peter Winstanley and the establishment of the Malawi–Liverpool–Wellcome Trust Centre for Clinical Tropical Medicine. Professor Stewart added that Tony Hart was a wonderful teacher who was hugely popular with both undergraduate and postgraduate students. This meeting therefore brought together a number of his former MD and PhD students, who described their work with him.

History of microbiology in Liverpool: a brief overview

Professor Malcolm Bennett (Dean of the Faculty of Veterinary Science, University of Liverpool) gave a brief history of microbiology in Liverpool. An early famous figure was William Duncan (born in 1805), a GP who saw the link between poor sanitation and disease some years before John Snow, and, of course, before Pasteur and Koch had developed the germ theory of disease. Alfred MacConkey, who gave his name to the medium still used in bacteriology laboratories, was also from Liverpool.

Since then, three outstanding microbiologists have emanated from the University of Liverpool: Alan Downie, Kevin McCarthy and, of course, Tony Hart. Alan Downie (born in 1901 in Aberdeen) took the chair of Bacteriology in 1943 and concentrated on research rather than diagnostics, setting the pattern for the future. His broad interests included smallpox and his work had great impact on the approach to vaccination. Kevin McCarthy (born 1921 in Liverpool) also initially worked on smallpox. On his return to Liverpool (after a sabbatical in Boston where he developed an interest in measles), he was instrumental in developing the first vaccinations for measles and rubella. What all three microbiologists had in common was an abundance of enthusiasm that they never lost throughout their careers. It was noted that Tony Hart was hugely supportive of his colleagues and encouraged staff to pursue their own research ideas.

Dr Derrick Baxby, a now-retired microbiologist and ex-colleague of Tony Hart, endorsed the importance of the continuity there had been at Liverpool. Many took for granted the opportunity to do one’s own research but this is not always so...
Session 1: herpes viruses

The opening session, chaired by Professor Tom Schulz (Hanover Medical School, Germany, formerly Professor of Genitourinary Medicine, University of Liverpool), addressed work on two herpes viruses, cytomegalovirus and herpes simplex.

Cytomegalovirus

Dr William Tong (Guy’s and St Thomas’ NHS Foundation Trust, London, and formerly Senior Lecturer in Virology, University of Liverpool) reviewed the ‘Prevention of Post-Transplant Cytomegalovirus Disease’. Cytomegalovirus disease is a significant cause of morbidity and graft loss in transplant patients. There had been two major developments in the last decade that have contributed to better prevention of post-transplant cytomegalovirus disease. The first, improved diagnostics, allows for the rapid quantification of the viral load of cytomegalovirus and the second is the availability of the oral antiviral agent, valganciclovir. Dr Tong described the advantages and disadvantages of two approaches to dealing with cytomegalovirus disease—pre-emptive therapy whereby antiviral therapy is used as soon as the viral load is seen to be increasing, as opposed to prophylaxis where antiviral therapy is used routinely post-transplant. The cost of drugs in pre-emptive therapy is lower and there is less risk of resistance to the drugs but the cost of monitoring cytomegalovirus levels can be high. On the other hand, there is an increased risk of resistance and late-onset cytomegalovirus disease with prophylaxis. He concluded that the best strategy would be a combination of the two approaches when applied to patients of different risk profiles. Dr Tong thanked Professor Hart for his support of this work.

Herpes simplex

Dr Stephen Kaye (St Paul’s Eye Unit, Royal Liverpool University Hospital) reviewed his work on ‘Herpes Simplex Keratitis’. Dr Kaye explained that herpes simplex virus type 1 (HSV-1) is a major cause of microbial keratitis, an infection of the cornea, and that it can lead to a profound loss of vision. He explained how, with the support and intellectual expertise of Professor Hart, they were together able to challenge the accepted dogma that HSV-1 could not establish a latent infection in the cornea of the eye. He addressed three important questions: (i) how does the virus get to the eye? (ii) does it remain in the eye and in what form? and (iii) can scarring and vascularization be reduced? The initial infection can be from droplet spread to the eye (‘front door route’) and this has been shown in mouse experiments to result in a high incidence of disease. An alternative or ‘back door route’ is from a non-ocular site, principally the mouth (where asymptomatic shedding from saliva is an important source of HSV-1), via the trigeminal ganglion towards the central nervous system and then to the eye. Latency is a feature of HSV infections and there is good evidence that HSV-1 can establish a latent infection not only in the trigeminal ganglion, but in the cornea itself. Reactivation and thus recurrence in the cornea leads to scarring and vascularization and in ~25% of cases, reduction in vision to below driving standards. Available antiviral agents include aciclovir and, more recently, valaciclovir and famciclovir. The latter two prodrugs, although having better bioavailability, are substantially more expensive than aciclovir. Aciclovir has proved to be effective both as therapy and for prophylactic use where it can reduce the risk of recurrent disease particularly in corneal transplant recipients. Dr Kaye finished by suggesting that possible future work could target corneal keratocytes that harboured latent HSV, with the aim of reducing recurrent disease.

Session 2: paediatric infections

The next session dealt with a range of paediatric diseases: respiratory syncytial virus (RSV) bronchiolitis, rotavirus gastroenteritis, meningococcal disease and typhoid fever. The session was chaired by Dr Luis Cuevas from the Liverpool School of Tropical Medicine.

RSV

Dr Paul McNamara (Institute of Child Health, Alder Hey Children’s NHS Foundation Trust, University of Liverpool) in his presentation ‘The Immuno-pathogenesis of RSV Bronchiolitis’, outlined the importance of RSV in infants under 1 year old. In total, 70%–80% of infants are infected with the virus before their first birthday; 60% of infants had a mild upper respiratory tract infection and 40% had both upper and lower respiratory tract infection. By their third birthday, all infants were infected with RSV. Global annual infection and mortality figures are 64 million and 160,000, respectively. RSV winter epidemics cause a spectrum of diseases ranging from mild upper respiratory tract symptoms and otitis media to severe life-threatening bronchiolitis. The focus of Dr McNamara’s work was to understand the immunological processes in the lungs of children with RSV bronchiolitis. This was made possible by Professor Hart’s long-term
collaborative relationship with Alder Hey Children’s Hospital and the work unveiled new insights into pulmonary immunological responses in children. The collection of bronchoalveolar lavage fluid from the lungs of infected children enabled study of the host response within the target organ. It was discovered that chemo-attractant cytokines predominated in the airways of infected children and these were identified and linked to the severity and progression of the disease. Further studies indicated that co-infection with a human metapneumovirus resulted in more severe disease. Prior to his death, Professor Hart had initiated a collaborative study in Recife, Brazil with the aim of determining what viruses were causing acute respiratory infections and whether the immunological responses in children with acute respiratory infection varied with the severity of the disease or the virus present. This work is ongoing.

**Rotavirus**

Dr Nigel Cunliffe (School of Infection and Host Defence, University of Liverpool) reviewed ‘Rotavirus Gastroenteritis in Children in Blantyre, Malawi’. Rotavirus infection is a leading cause of global mortality from diarrhoeal disease in children under 5 years of age, accounting for over half a million childhood deaths each year, with >80% of these deaths occurring in Africa and Asia. In the mid-1990s, under the guidance of Professor Hart, Dr Cunliffe secured a Wellcome Trust Research Training Fellowship that allowed him to initiate a major study of rotavirus infections in Malawi. The aim of the work was to examine the importance of rotavirus among hospitalized Malawian children with diarrhoea, to examine the clinical interaction of rotavirus with HIV infection and to investigate the age distribution, seasonality and strain types of rotavirus that were circulating. Rotavirus was confirmed to be a leading cause of severe diarrhoea among Malawian children, but disease severity was not increased by host infection with HIV. In studies conducted from 1997 to 2007, rotavirus was detected in a third of >3000 Malawian children hospitalized with diarrhoea. Reverse transcription–polymerase chain reaction methodology was used to genotype the strains. An interesting finding was that although some rotavirus strains were of globally prevalent types, globally uncommon strains (notably serotype G8) were identified in a surprisingly large number of cases. Dr Cunliffe concluded by saying that rotavirus vaccines have great potential to substantially reduce the morbidity and mortality associated with diarrhoeal disease among children in Malawi, but that they will need to protect infants at a young age and against a wide range of rotavirus serotypes.

**Meningococcal disease**

Dr Andrew Riordan (Alder Hey Children’s NHS Foundation Trust, Liverpool) in his talk ‘Meningococcal Disease in Children’ presented work from the Liverpool Meningococcal Group. Meningococcal disease is the commonest infectious cause of death in childhood in developed countries and can present as septicaemia, meningitis or a combination of both. Research into this important disease had been led by Professor Hart and started more than 20 years ago at Alder Hey Children’s Hospital. A key factor in understanding the disease was determining whether the pathogenicity of the organism or the susceptibility of the host was more important. Bacterial load and production of endotoxin are contributors to the pathogenicity of the bacterium while host factors include cytokines, chemokines, neuropeptides and adhesion molecules. This work on the pathogenesis of the disease has revealed details of the microcirculation of children with severe disease. These variables correlate well with clinical recovery, Dr Riordan also explained that this work has allowed the group to help devise evidenced-based guidelines for managing meningococcal disease in children, a fitting output after 20 years of work in this area.

**Typhoid fever**

Dr Christopher Parry (School of Infection and Host Defence, University of Liverpool) gave an overview of ‘Typhoid Fever’. This work is another example of collaborative studies on this worldwide infectious disease between Professor Hart’s group in Liverpool and colleagues in Bangladesh, Pakistan and Vietnam. Typhoid is caused by Salmonella enterica serotype Typhi and serotype Paratyphi A, and remains an important global problem with an estimated 27 million cases of enteric fever in the world each year, with >200000 deaths. The burden of disease in Asia is particularly high but travellers returning to the UK are also affected with >400 culture-positive cases in England and Wales each year. Paratyphi A is an increasing problem in some areas. Appropriate antimicrobial therapy can result in mortality rates below 1%. Unfortunately plasmid-mediated resistance to several valuable first-line drugs, chloramphenicol, ampicillin and co-trimoxazole is widespread in many endemic areas. In addition, decreased susceptibility to fluoroquinolones, due to chromosomal mutations, is widespread in Asia and infections with such isolates respond poorly to ciprofloxacin and ofloxacin. Possible alternatives include new-generation fluoroquinolones, extended-spectrum cephalosporins and azithromycin, but resistance continues to increase. If extended-spectrum β-lactamase (ESBL) enzymes were to spread into Typhi and Paratyphi A, this would leave few other antimicrobial options available. Dr Parry concluded that although effective vaccines are available for typhoid, there are none for paratyphoid. There is an urgent need for the programmatic use of vaccination as a public health tool in endemic areas.

**Session 3: zoonoses**

The final session of the day centred on zoonoses and was chaired by Professor Malcolm Bennett (NCZR, University of Liverpool). The topics included non-typhoidal Salmonella in Kenya, resistance to antimicrobials, Cryptosporidium and emerging infections.

**Non-typhoidal Salmonella**

Dr Sam Kariuki (Kenya Medical Research Institute, Nairobi, Kenya) in his talk entitled ‘Epidemiology of Non-typhoidal Salmonella in Kenya’, described how the Institute, in collaboration with Professor Hart, had carried out sentinel surveillance on cases of bacteriaemia in children below 5 years of age admitted to hospitals in Nairobi and in a rural district hospital over a period of 15 years. In this population, disease caused by non-typhoidal Salmonella is second in importance only to infections with Streptococcus
pneumoniae. The survey revealed that non-typhoidal Salmonella was present in 18% of children with febrile illness and resulted in 28% mortality. The predominant serotype was Salmonella Typhimurium. There was an association of the incidence of non-typhoidal Salmonella with younger age and with socioeconomic status. Resistance to antibiotics is a problem, occurring in 45% of isolates. All the non-typhoidal Salmonella isolates remained fully susceptible to ceftriaxone and ciprofloxacin. It is probable that disease caused by Haemophilus influenzae type B and S. pneumoniae will decrease in incidence in Kenya with the introduction of vaccines against these infections. Non-typhoidal Salmonella will thus continue to dominate as a cause of bacteraemia and meningitis among vulnerable populations, and a gradual increase in the incidence of multiple drug resistance will pose an increasing threat. Dr Kariuki finished by outlining the unknown factors in non-typhoidal Salmonella disease. These include a lack of knowledge about the host and pathogen basis for the increased invasiveness seen in the non-typhoidal Salmonella strains, the source or reservoir of infection in the community and the possibility of human to human transmission. Most importantly, a vaccine to prevent infection by non-typhoidal Salmonella is currently lacking.

**Antimicrobial resistance**

Dr Susan Dawson and Professor Malcolm Bennett (NCZR, University of Liverpool), jointly gave a presentation on ‘Antimicrobial Resistance’. Antimicrobial resistance is an increasing problem in both human and veterinary medicine, and some believe that the use of antimicrobials in animals may be responsible for this increase. The source of such resistant strains, their dynamics and the persistence of resistance are not understood outside the clinical setting. Professor Hart was instrumental in initiating studies on antimicrobial resistance in wildlife, domestic livestock and companion animals and relating findings to human medicine. Antimicrobial resistance was found to be common in the normal bacterial flora of wildlife, even those without apparent exposure to anthropogenic sources. The prevalence of this resistance varies between individual animals, host species, environment and time of year, but there are no clear associations with contact with livestock or the intensity of farming. Two important causes of nosocomial infection in humans (and now also increasingly associated with disease in the community), namely methicillin-resistant Staphylococcus aureus (MRSA) and ESBL-producing Escherichia coli, have also been investigated in animals. MRSA strains can be found in dogs and these reflect those most prevalent in the human population, although strains isolated from horses are uncommon in the human population. However, the prevalence of nasal carriage of MRSA in dogs and horses outside of veterinary hospitals is very low. ESBL-producing E. coli are not common in the faeces of dogs, but have been found in the faeces of hospitalized horses. As with MRSA, these strains are not the same as the predominant types found in people. ESBL-producing E. coli have also been found in farm animals, particularly dairy cattle.

**Cryptosporidiosis**

Dr Emily Hotchkiss (Moredun Research Institute, Midlothian, Scotland), in her talk ‘Cryptosporidium—From Children in Malawi to Calves in Cheshire’, presented an account of the work she and Professor Hart had been involved with. She noted that this work exemplified Professor Hart’s approach to his working life: inclusive, far-sighted and innovative. The initial work focused on the laboratory identification of oocysts and details of the pathogen in children in Liverpool hospitals, and culminated in highlighting the zoonotic potential of cryptosporidiosis. Cryptosporidium spp. are the fourth most common cause of gastroenteritis in humans, with HIV-infected individuals being more likely to have zoonotic genotypes than uninfected people. The development of novel molecular tools within the group in Liverpool has aided the study of cryptosporidiosis in children in developing countries and latterly in the UK. Dr Hotchkiss described the studies she has carried out with Professor Hart examining the prevalence, risk factors, distribution and zoonotic potential of genotypes and sub-genotypes of the parasite in calves on farms in Cheshire. The results indicate that zoonotic Cryptosporidium parvum is prevalent in the area, that there is local transmission of the organism and that unweaned calves are an important reservoir of the infection on farms. This work has been further extended to include consideration of social/contact networks between farmers. These projects reflect part of the extensive collaborations with the Veterinary Faculty that have led to the establishment of the NCZR, a great legacy for the future.

**Emerging infections**

Dr Dilys Morgan (Health Protection Agency Centre for Infections, London) gave an update on ‘Emerging Infections—Detecting and Assessing the Threat’. She began by describing the numerous infections, many of which were previously unknown, to emerge since the 1970s. Other infections can emerge from a change in an existing infection (e.g. multidrug-resistant bacterial infections) or a known infection spreading to a new area or population (for example West Nile Fever). Dr Morgan used a number of serious infections to illustrate the problems that arise at the animal–human interface—the first was BSE/CJD in the UK. This emerging infection had a huge impact on industry, estimated at greater than £3 billion/year and resulted in a lack of confidence in the authorities by the public. Two key factors emerged for the government with regard to this outbreak: how to handle a hazard and to communicate risk. Another emerging disease, West Nile Fever, spread rapidly in the USA between 1999 and 2006, after which the infection became endemic. In the UK a contingency plan was drawn up in 2004, but the disease has not yet been found, raising the question of whether surveillance activities should be maintained. Dr Morgan then described the problems associated with monkeypox in the USA, which was originally discovered during the smallpox eradication programme in Africa and had not been seen previously in the Northern hemisphere. A key point about this infection in the USA is that cases were derived from contact with prairie dogs that had been housed or transported with a consignment of ‘exotic rodents’ imported from Ghana. This highlighted the public health threat from imported exotic animals, as they can carry non-indigenous zoonotic pathogens that may spread rapidly in a susceptible population and that may also result in interspecies spread. Dr Morgan concluded by emphasizing that since most emerging infections are zoonotic in origin, assessing the zoonotic potential of animal infections is crucial.
Concluding remarks

The meeting finished with concluding remarks from Professor Bernard Brabin (Liverpool School of Tropical Medicine) who reflected that the day had clearly illustrated the wide range of collaborations and co-operation between Tony Hart and many local, national and international research groups, covering diverse aspects of science. Through this enthusiasm he helped many young investigators in diverse ways. Professor Brabin further emphasized that Tony Hart was also a great teacher, who played a key role in helping Professor Osamu Nakagomi establish a formal Masters course in Tropical Medicine in Nagasaki University, Japan and that he also helped establish a course in Tropical Paediatrics at Amsterdam University for paediatric residents and regularly taught on it. His research links with Brazil, alluded to in earlier talks, were equally fruitful and provided a significant opportunity for a teaching role there. The main Paediatric Department laboratories in Recife have been named after him.

Continuing medical education (CME)

The meeting was granted CME recognition (6 credits) by the Royal College of Pathologists of the United Kingdom.

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Transparency declarations

None to declare.