Current topic

Paediatric infectious diseases: some recent advances and future priorities

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Infectious diseases present an ever changing panorama. While change and advance are not synonymous, changes in human behaviour—by presenting urgent new dilemmas—may lead to advances in understanding of disease and its transmission. The first decade of awareness of the illness now known to be due to the human immunodeficiency virus (HIV) will have been remarkable in this respect. Some of the advances in childhood infectious illness that have also occurred in the last 10 years or so together with some future priorities, inevitably personal ones, will be reviewed here.

Some recent advances

‘NEW’ INFECTIOUS ILLNESSES

Most are diseases known to paediatricians for many years that have been linked to a causal infecting organism for the first time. Others appear to be new illnesses, or at least recently recognised as occurring in children as well as adults. They are listed in the table. It is possible to consider only some of them further.

Haemolytic uraemic syndrome

In addition to the now well known enteropathogenic, enterotoxigenic, and enteroinvasive strains of *Escherichia coli*, an enterohaemorrhagic variety has been reported, which produces cytotoxins.⁴ These are known either as Shiga like toxins, being very similar to that produced by *Shigella dysenteriae* type 1, or as verotoxins, Vero cells being used to detect their cytotoxic nature. A particular serotype of one of them, 0157:H7, seems likely to prove an important aetiological agent for both haemolytic uraemic syndrome (a triad of haemolytic anaemia, thrombocytopenia, and acute renal failure), in which the Shiga like toxin may cause the initial endothelial damage, and haemorrhagic colitis.¹⁷ The recent occurrence of the haemolytic uraemic syndrome and

Table Infectious illnesses

Illness	Newly recognised infecting organisms
Long recognised:	
Cat-scratch disease	Pleomorphic Gram negative bacillus ¹ (not yet named)
Erythema infectiosum (fifth disease)	Parvovirus B19 ^{2, 3}
Aplastic crisis	
Fetal hydrops	
Haemolytic uraemic syndrome and haemorrhagic colitis	Enterohaemorrhagic <i>Escherichia coli</i> 0157:H7 ⁴
Infectious diarrhoea	Adenovirus, ⁵ <i>Aeromonas hydrophila</i> , ⁶ <i>Campylobacter</i> spp., ⁵ <i>Cryptosporidium</i> spp., ⁵ <i>Yersinia enterocolitica</i> , ¹⁵ <i>Legionella pneumophila</i> ⁷ <i>Chlamydia trachomatis</i> ⁸ <i>C psittaci</i> (TWAR strain) ^{9, 10} Human herpesvirus-6 ¹¹
Respiratory tract infection	
Roseola infantum (exanthem subitum)	
Newly recognised in children:	
Acquired immunodeficiency syndrome ¹²	Human immunodeficiency virus (HIV)
Infant botulism ^{13, 14}	(<i>Clostridium botulinum</i>) <i>C barati</i> , <i>C butyricum</i>
Lyme disease ¹⁵	<i>Borrelia burgdorferi</i>
Toxic shock syndrome ¹⁶	<i>Staphylococcus aureus</i> exotoxin (TSST-1)

variants of thrombotic thrombocytopenic purpura in three siblings¹⁸ supports the suggestion¹⁷ that the latter should also be included.

Respiratory tract infections

Chlamydial infections have been of more importance to children in the past decade than those due to *Legionella pneumophila*. Respiratory infections in young infants associated with maternally transmitted *Chlamydia trachomatis* were first described a

little over 10 years ago,⁸ and although chlamydial cervicitis and urethritis are now the commonest sexually transmitted infections in the United Kingdom, chlamydial pneumonitis is almost certainly underdiagnosed in young infants. Perhaps a few such cases are associated with sudden unexpected infant deaths.

In the last few years outbreaks of pneumonia have been reported in adolescents and young adults due to a strain of *Chlamydia psittaci* known as TWAR (TW for Taiwan where it was first isolated, AR for acute respiratory).⁹ It seems as if this particular infection has a human spread, rather than the avian to human one of psittacosis. It may turn out to be relatively common, resembling infections associated with *Mycoplasma pneumoniae*.¹⁰

The acquired immunodeficiency syndrome (AIDS)

This has received more attention in the past few years than any other infection. Criteria for its diagnosis, that of the AIDS related complex in children,¹⁹ and for diagnosis of perinatal transmission²⁰ have been drawn up. The number of those 14 years or less with AIDS in the United Kingdom at the end of 1987 was still very small (n=19), maternal transmission appearing likely in over two thirds.²¹ Over 10 times as many children were HIV positive, one third of whom were haemophiliacs or other recipients of blood or blood components. In the AIDS cases pneumonia was the commonest presenting diagnosis, followed by encephalopathy. The number of HIV antibody positive women 15 years and older—the mothers of today and tomorrow—is, however, increasing fast. They constitute one 10th of all such cases in the United Kingdom, and one quarter of them are in Scotland.²¹ A report from the European Collaborative Study of 271 children born to HIV infected mothers in eight European centres recorded a 24% transmission rate, but cautioned this was likely to be an underestimate, as follow up was still short.²²

Lyme disease

Erythema migrans with other complications after a tick bite was recognised in parts of Europe in the first half of the century. But a small New England town—Lyme—has now given its name to this illness. Astute physicians realised that rather than too many children living near each other there were being diagnosed as suffering from 'juvenile rheumatoid arthritis'.²³ Eventually a newly discovered spirochaete, *Borrelia burgdorferi*, was incriminated as causing their illness.¹⁵ Ticks of the *Ixodes* spp were the likely vectors. After the tick bite, and the often resulting migrating erythema, central nervous system signs such as lower motor neurone facial palsies,

with cerebrospinal fluid pleocytosis, and recurring arthralgia may complete the picture. The illness sometimes follows a prolonged course. Its recognition in children in this country was first reported from Southampton.^{24 25} The deer of the nearby New Forest were accused of harbouring the infected ticks; it is now known that dogs and cats living in regions where the disease is endemic may also carry the ticks.

Toxic shock syndrome

Though usually thought of as a disease confined to women using tampons, it may occur in younger children.¹⁶ It is important for paediatricians to keep this syndrome in mind for the accompanying hypotensive shock is its most dangerous feature. Restoration of circulating blood volume is urgently needed and careful monitoring of arterial and central venous pressure.²⁶ Blood cultures are usually negative, but the syndrome is caused by a particular exotoxin of *Staphylococcus aureus*, called TSST-1.

ADVANCES IN UNDERSTANDING OF HOST DEFENCE

The rare inherited defects and childhood immunodeficiency disorders—of which most of us see very few examples in our professional lifetimes—have given immunologists the opportunities for making rapid advances in understanding host defence. An appreciation of how the component parts integrate to form the whole has accelerated in the past 10 years. Most of us have great difficulty in interpreting these advances, and struggle with often changing nomenclature and articles written in language we find difficult or impossible to understand. It may be helpful to summarise, in barest outline, the most fundamental aspects.

Humoral immunity depends on the ability of the short lived polymorphonuclear neutrophils to engulf bacteria and kill them with the help of the multi-enzyme complement cascade. It also depends on antibodies produced by B lymphocytes (which mature in fetal liver and bone marrow) and acute phase reactants such as C reactive protein.²⁷ The neutrophil's central role depends on five important stages—activation, deformation, chemotaxis, phagocytosis, and the killing process—the individual parts of each now almost entirely understood.²⁸ Complement and antibody are crucial for fully effective neutrophil function. The complement system may be triggered via antibody through its classical pathway, or through its alternative pathway directly by the infecting organism.

Cell mediated immunity relies on the longer lived macrophages (also phagocytic), which are best able to cope with the few bacterial species, and with viruses and protozoa, which live within host cells; on

lymphokines (products of activated lymphocytes which include the interferons, interleukins, colony stimulating factor, and tumour necrosis factor); and on T (thymus maturing) lymphocytes.²⁷

The immune system cannot know in advance what it is going to meet. Thus antigen receptors (antibodies) of a wide variety have developed on the surfaces of B lymphocytes in order to deal with the potentially very large number of foreign antigens, only one receptor being expressed on each cell. When antigen binds with its complementary receptor antibody, the cell becomes activated, there is clonal proliferation and maturation to antibody forming plasma cells, so that large concentrations of the antibody can be produced. Some of the activated B lymphocytes become non-dividing memory cells, and it is these which will be able to mount the faster and more effective secondary immune response should the original antigen be met again in the future.²⁷

T cells, more concerned with the control of intracellular infection, also, like B lymphocytes, have their individual but structurally different antigen receptors that have the ability to recognise antigen and produce memory cells. There are two main subsets of T cells, the helper/inducer cells (CD4, CD standing for clusters of differentiation, previously T4), and the cytotoxic/suppressor cells (CD8, previously T8). T helper cells recognise cell surface antigens in association with molecules of the class II major histocompatibility complex, and release gamma interferon to activate macrophages. The cytotoxic T cells are concerned with class I major histocompatibility complex on the surface of cells infected by virus, which can kill the virally infected cells before they replicate.²⁷

Antibody formation by B lymphocytes needs the collaboration of the CD4 cells. It is the latter that are the primary target of the HIV; as they are lost progressively, so the ability to secrete antibodies is lost. The activity of suppressor T cells is uppermost in the newborn infant, and presumably through most of fetal life.²⁹ Thus there is a suppression of B cell differentiation to B cells and antibody production. The newborn infant also has deficiencies of complement and of certain antibodies—both exaggerated by preterm birth—so that his neutrophil response is less than efficient. Activation is poor, so there is little increase in surface receptors on the cell, and less ability to stick. The cells are unusually rigid, so their ability to adhere to surfaces or move through vascular endothelium to the site of infection is compromised, and hence chemotaxis is slower. Phagocytosis, the ability to engulf micro-organisms, may be normal in otherwise healthy infants, but in stressed or infected infants it is less effective. And

the relative lack of enzymes needed for the respiratory burst that generates toxic oxygen radicals such as superoxide and hydrogen peroxide may lead to defective killing.³⁰ Further, if experimental work is relevant to the human, bone marrow reserves may be easily exhausted so that the infected infant becomes neutropenic.³¹

ADVANCES IN LABORATORY DIAGNOSIS

Tests for antibody such as the enzyme linked immunoadsorbent assay (ELISA), for antigen such as latex agglutination, and for endotoxin such as the limulus lysate test, have been more widely applied in recent years. The first two may be very useful for quick confirmation of the diagnosis when a certain micro-organism is suspected. Then the acute phase reactant C reactive protein—first found in the serum of patients with pneumonia in the 1930s—has attracted renewed interest recently, with greatly improved and reasonably rapid quantitative methods available for its detection. Its greatest use may be in following the course of an infection rather than in early diagnosis.

But it is in molecular biology that we have not only one of the fastest growing areas in medicine but one which, when it has realised its full potential, will be of enormous benefit in the field of infectious diseases.³² Techniques such as monoclonal antibody production (commercially exploited to make large amounts of specific antibody available), protein biochemistry, and recombinant DNA technology probably benefit diagnosis more than treatment at present. The characterisation of bacterial DNA and proteins has meant simpler ways of typing organisms. Plasmid DNA isolation, and the recognition of specific sequences of DNA with DNA probes, are being used in clinical microbiology, often elucidating the epidemiology of outbreaks of infection.³³

Routine microbiology laboratories in many hospitals may not be able to offer all these services but will know where they are available. Clinicians need therefore to be aware of what is possible, and to keep in close touch with their microbiologist colleagues. Talking over clinical problems with them, and ensuring they get the fullest information possible about patients' illnesses, will bring its rewards.

ADVANCES IN TREATMENT

Antiviral drugs

The two which seem to have emerged as potentially the most promising where childhood infections are concerned are acyclovir and ribavirin. Ganciclovir still needs further evaluation. Acyclovir will be most useful for treatment of herpes simplex virus infections either in the neonatal period (where vidar-

abine is another possibility), or in the immunocompromised child for whom it may also be needed for varicella zoster infections.

Respiratory illness is the main reason for hospital admission in children under 5 years of age, and the major cause of it is respiratory syncytial virus. The organism is also frequently responsible for hospital cross infection. While deaths in otherwise healthy infants are now very unusual, respiratory syncytial virus infections may have a fatal outcome in infants with congenital heart disease, especially when accompanied by pulmonary hypertension, and in immunocompromised children. Ribavirin is particularly active against RNA viruses—especially respiratory syncytial virus and parainfluenza. A case can be made for the use of aerosol ribavirin in immunocompromised children and those with congenital heart disease and bronchopulmonary dysplasia if they have proved infection with either of those two organisms. But large multicentre trials are surely justified before this very expensive drug is used on a large scale,^{34 35} as previous trials have involved relatively small numbers only.

ORAL REHYDRATION THERAPY FOR DIARRHOEA

This is an important advance which has been responsible for the yearly saving of half a million children's lives. Ebrahim points out that despite this, it is still used by a minority of the population in developing countries.³⁶ Even in the United States there are an average of 500 deaths yearly from diarrhoea; and the oral glucose electrolyte solutions are frequently not prescribed by paediatricians there, nor used by parents.³⁷ The same may be true in this country.

INTRAVENOUS IMMUNOGLOBULIN

The results of trials of intravenous immunoglobulin in children with AIDS, and with mucocutaneous lymph node syndrome (Kawasaki disease) have been favourably reviewed.³⁸ As a causal organism of this latter supposedly infectious illness is still unidentified, this treatment must be regarded as empirical. Small trials of the use of immunoglobulin (intravenous and intramuscular) have also been carried out in the neonatal period, either as a therapeutic measure in infants with suspected or later proved bacterial infection, or both,³⁹ or as a preventive measure in preterm and low birthweight infants.^{40 41} These trials have suggested some benefit for its use, as has one trial using an IgM enriched intravenous preparations.⁴² These studies are careful and important contributions, but large scale multicentre trials are necessary. The preparations need to be refined to be of most benefit against likely infecting organisms causing neonatal

infection; the duration of their beneficial effects needs to be worked out, and it is important to be certain they will not interfere with normal responses to routine immunisations. The development of non-A non-B hepatitis in adult trials of intravenous immunoglobulin has been reported, but should be avoidable. Long term safety needs to be ensured before the immunoglobulins are used on a wide scale in neonatal units. These preparations, however, are more easily available than granulocytes for transfusion, which have also undergone small controlled trials, but similarly need large multicentre ones.⁴³ If both forms of treatment were proved safe in the short and long term, a combination of the two might be more logical on immunological grounds.

ADVANCES IN PREVENTION

The eradication of smallpox in 1979 must surely be recognised as an outstanding achievement by the World Health Organisation (WHO). Enormous credit is due to those responsible for the planning and implementation of what must have seemed an almost insuperable task.

Serious *Haemophilus influenzae* type b infections affect one in 200 American children in the first five years of life,⁴⁴ and their prevalence in this country is rising. The organism is one of the preschool child's most dangerous pathogens. A capsular polysaccharide (polyribosyl-ribitol-phosphate) vaccine was licensed for use in the United States in 1985 after trials. Although it will not protect the youngest children (antibody responses are poor until about 18 months of age), and will have no impact on non-typable strains which account for a sizeable proportion of upper respiratory tract infections,⁴⁴ it has been assessed as being cost effective.⁴⁵ Further trials, with other vaccines aimed at protecting younger infants, are being carried out in several countries.

Hepatitis B vaccine is to some extent unique in that if it could be given to all infants born to women carrying the hepatitis B surface antigen, not only is there the prospect of preventing chronic hepatitis, but, perhaps, hepatocellular carcinoma as well.

Some future priorities

IMMUNISATION

Universal childhood immunisation is one of the four priorities selected by the United Nations Children's Fund (Unicef) in collaboration with the WHO in their drive to improve the health and nutrition of the world's children. The Director General of WHO has been reported as saying that in 1987 just half of the latter were now receiving immunisation against

poliomyelitis, diphtheria, pertussis, tetanus, measles, and tuberculosis; the expanded programme was judged to be preventing more than one million deaths from measles, neonatal tetanus, and pertussis, and more than 175 000 cases of poliomyelitis. But the goal of health for all by the year 2000 still faces enormous difficulties in the poverty stricken parts of the world.

The United Kingdom certainly has its own house to put in order too. Given that uptake of immunisation is least in urban areas,⁴⁶ primary health care teams there need to know that it is primarily *their* informed attitudes and enthusiasm, backed by efficient organisation, which lead to the desired high uptake.⁴⁷ It is easy to blame non-compliance or non-completion of schedules on socioeconomic factors, but this is probably unjustifiable.⁴⁸ There is no reason for health professionals in this country not to be well informed about the very few contraindications to immunisation existing. Copies of the recently distributed green book⁴⁹ need to be in every health clinic, and on the desks of general practitioners and paediatricians. The information is clearly set out, should allow those responsible to speak with one voice, and prevent confidence being undermined by the wide coverage given to every pronouncement of the anti-immunisation lobby. The new measles, mumps, and rubella vaccine introduced in October 1988 needs a 95% uptake to eradicate these rarely (at least in this country) lethal, but occasionally very disabling infections. A spirit of healthy competition between districts to achieve such levels for *all* immunisations in children would not go amiss.

PREVENTION OF CHORIOAMNIONITIS ASSOCIATED PRETERM BIRTH

It may seem out of place to discuss this primarily maternal infection here, but I think paediatricians will have to take the lead in urging obstetricians to take chorioamnionitis more seriously. This inflammation of the decidua, fetal membranes, and umbilical cord is mostly clinically silent. It is only diagnosed by pathologists if they decide to look for it and if they receive the placenta in the first place. But it is at its most prevalent at low gestations, and there is increasing suspicion that it is a cause rather than a sequel to premature rupture of the membranes in many cases.⁵⁰ The most common infecting organism may well turn out to be *Ureaplasma urealyticum*.⁵¹ This is an organism of low virulence (except as we have learned recently for very immature babies⁵²), and it can flourish in amniotic fluid for several weeks. Certain bacteria, of which the ureaplasmas are prime examples, produce phospholipase A₂, an enzyme necessary for the forma-

tion of arachidonic acid. This in turn is a substrate for prostaglandin synthesis, and prostaglandin is involved in the initiation of labour.⁵⁰ Epidemiological surveys to discover precisely who is at risk, and large multicentre trials of possible treatments, are badly needed. Time spent on chorioamnionitis might ultimately prove very rewarding. Many surviving infants of extremely low birth weight have required weeks of intensive care, and later outcome is not always the unqualified success story many would have us believe. If the babies could stay inside the uterus *safely* for longer, they, their parents, and their nurses and doctors would surely be grateful.

URINARY TRACT INFECTION

It goes without saying that earlier diagnosis would do much to improve results. About half the children receiving dialysis for renal failure are in this unenviable situation because their renal failure is secondary to scarring and chronic atrophic pyelonephritis. Such involvement of the renal parenchyma is also an important cause of hypertension. The infections which will lead to these end results are usually acquired in infancy or well before 5 years of age, when reflux is present. Each child that is hypertensive or dialysed for this reason must represent a failure of early diagnosis, or of effective treatment, or of failure to prevent recurrence, relapse, or reinfection. The younger the child, the more non-specific are symptoms of urinary tract infection likely to be, and no clinical examination of such infants can be complete without urinalysis and culture of a satisfactorily collected and processed specimen. If this really fundamental component of good medicine was conscientiously practiced, if all children with diagnosed urinary tract infection were properly investigated, treated, and kept under long term surveillance, much subsequent illness and disruption of family life could be avoided.⁵³

HEALTH EDUCATION

Sexually transmitted diseases started to rise steeply in frequency from the 1960s; this was partly due to improved diagnosis. Promiscuous sex from an early age may lead to carcinoma of the cervix, impaired fertility, or be the cause of sometimes disabling, occasionally lethal infections in infants born to mothers infected with certain sexually transmitted organisms. The suggestion of Curtis and colleagues that sex education should be taken very much more seriously is surely important,⁵⁴ and this difficult and sensitive task may need the involvement of paediatricians.

CONTROL OF INFECTION

In his review of treatment of diarrhoeal diseases in

developing countries, Ebrahim pointed out that education about washing the hands can lead to an 85% reduction of secondary attack rates of diarrhoea within families.³⁶ With an increasing population of preschool children at nurseries and play groups in this country such education is also of profound importance for staff working there, and by example for the children. It is not only gastrointestinal pathogens that may be transmitted via the hands, but certain respiratory tract pathogens as well. In hospital too, effective hand washing conscientiously practised by all staff would do much to reduce the very considerable burden of nosocomial infection there. The increasing numbers of infections with *Salmonella* spp and with *Listeria monocytogenes* now occurring are likely to be of serious importance to newborn infants and immunocompromised older children. An asymptomatic and unsuspected carrier mother may transfer salmonella to her newborn infant. He or she is then frequently the index case for neonatal unit epidemics. While the mother with listeriosis is more likely to be febrile and have some malaise as a warning, this is not invariable. Only effective infection control measures will prevent these epidemics occurring.

There is an urgent need for more paediatricians to make infectious diseases a special interest. The subject will always be of special importance for children. The possibilities for accurate diagnosis and effective treatment, and the opportunities for prevention, have never been greater.

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