Reviews in Medicine

Paediatrics – Part II

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Steroids and meningitis

The use of steroids in meningitis has been the subject of recent debate. Trials in the 1960s failed to show any beneficial effects on neurological outcome from the use of methyl prednisolone.¹²¹ Five controlled studies have now been published which suggest that dexamethasone is beneficial in improving the outcome in bacterial, primarily *Haemophilus influenzae* meningitis, particularly for sensorineural deafness.

Lebel *et al.* in three double-blind placebo-controlled trials in the USA,^{122,123} have compared cefuroxime or ceftriaxone combined with either placebo or dexamethasone. 0.15 mg/kg/dose 6 hourly intravenously for 4 days. In the first two trials involving 200 children, three beneficial effects were seen, firstly a reduction in cerebrospinal fluid (CSF) lactate and protein levels and a rise in CSF glucose compared to control at 24 hours. Secondly, duration of fever was significantly shorter (1.6 vs 5 days, $P < 0.001$), and thirdly the frequency of moderate, severe or profound hearing loss was significantly reduced (3/92 dexamethasone vs 13/84 placebo, $P < 0.01$). There were too few cases of meningitis from causes other than *H. influenzae* to be statistically certain that dexamethasone was of general benefit. A further 60 patients were studied, which confirmed their earlier results. In a non-placebo-controlled trial, 428 Egyptian patients (children and adults) were assigned to receive either ampicillin plus chloramphenicol alone or in combination with dexamethasone.¹²⁴ A significant reduction in case fatality was observed in patients with pneumococcal meningitis receiving dexamethasone, and dexamethasone-treated patients showed a reduction in neurological sequelae and hearing loss. Another study¹²⁵ reviewed the outcome in 97 patients treated for pneumococcal meningitis between 1984 and 1990, of whom 39 had received dexamethasone (0.15 mg/kg/dose 6 hourly for 4 days). Although results for reduction

in hearing impairment associated with dexamethasone did not achieve significance, when neurological sequelae overall were examined, dexamethasone showed a statistically significant beneficial effect (4/35 vs 14/43, $P = 0.033$).

In experimental models of *Streptococcus pneumoniae* and *H. influenzae* meningitis, dexamethasone has significantly reduced CSF pressure, brain oedema, and CSF lactate concentrations, reduced leakage of low molecular weight proteins from the serum to CSF and, when given prior to antibiotic therapy, has significantly reduced CSF levels of tumour necrosis factor α (TNF- α) and other indices of meningeal inflammation. CSF levels of prostaglandin E₂ (PGE₂) and interleukin-1 β (IL-1 β) have been shown to be significantly lower in dexamethasone-treated patients with meningitis.^{126,127} In a recent placebo-controlled trial in 101 Costa Rican children,¹²⁸ cefotaxime with dexamethasone (0.15 mg/kg/dose 6 hourly for 4 days) was compared with cefotaxime plus placebo, with the dexamethasone given 15–20 minutes prior to the first dose of cefotaxime. Improvement within 12 hours occurred in mean CSF opening pressure and estimated cerebral perfusion pressure, and concentrations of TNF- α and platelet activating factor had decreased in the steroid treated group, but increased in the controls. Duration of fever was less in the steroid treated group. At follow-up significantly fewer dexamethasone-treated children compared to controls had one or more neurological or auditory sequelae (7/51 vs 18/48, $P = 0.007$), with a relative risk of sequelae for a child receiving placebo compared to dexamethasone of 3.8. The reduction in hearing impairment with dexamethasone did not achieve significance (3/50 vs 7/44, $P = 0.18$).

Methodological problems exist in these trials, e.g. the lack of a placebo control in Girgis' study¹²⁴ and in Lebel's¹²² studies, the use of different antibiotics may have contributed to difference in outcome. The unusually high incidence of hearing impairment following meningitis reported in that trial is noted. However it now seems probable that anti-inflammatory therapy with dexamethasone

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reduces the mortality and long-term consequences of bacterial meningitis, and dexamethasone has been recommended as part of the treatment for *H. influenzae* and *S. pneumoniae* meningitis.^{129, 130} It is possible that adverse effects of steroid treatment may become more apparent. In Lebel's series, two patients developed gastrointestinal haemorrhage, and one showed delayed sterilization of the CSF with cefuroxime and dexamethasone treatment. Although caution has been urged by some until further large-scale trials have been performed, a recent poll of American paediatricians found four out of five in favour of dexamethasone therapy for meningitis,¹³¹ making it difficult to withhold the drug.

Monoclonal antibody therapy

Technological changes over the last 30 years have had no measurable impact on the mortality from meningococcal infections in children.¹³² A new and potentially promising adjunctive therapy for meningococcaemia and Gram-negative sepsis now awaits full evaluation in children. HA-1A is a monoclonal antibody directed against the lipid A of endotoxin. In a double-blind randomized placebo-controlled trial in 543¹³³ adults, HA-1A significantly reduced the 28 day mortality for patients with proven Gram-negative sepsis (placebo 49% vs HA-1A 30%, $P = 0.014$) and still significantly reduced the mortality when shock was present (57% placebo vs 33% HA-1A, $P = 0.017$).

Experience in children is limited. No efficacy data from controlled trials exist for children, but the drug has been administered to well over 100 children, including neonates and premature infants on a named patient basis and in open trials. Doses used have been 3 mg/kg for sepsis and 6 mg/kg for fulminant meningococcaemia, to a maximum of 100 mg in both settings. The incidence and type of adverse reactions were similar to those reported in adults, which are of the order of 1–2% and manifest as hypotension (17/1,158, 0.95%), and hypersensitivity type reactions (flushing, erythema, oedema and urticaria, 6/1,158, 0.5%). In an open trial in North America, of the 2,800 patients enrolled, eight were less than 16 years and received 6 mg/kg.¹³⁴ One patient, a 10 year old boy, had transient hypotension that resolved without treatment or stopping the infusion. There is one published report¹³⁵ of an 8 month old infant with overwhelming meningococcaemia and shock with deteriorating course, who made significant clinical improvement within 12 hours of receiving 6 mg/kg of HA-1A, and was discharged at day 10 with full recovery. In Europe, seven children have received HA-1A for fulminant meningococcaemia at a dose of 6 mg/kg. There was only one death which was

less than the 50% mortality predicted from prognostic scoring systems, and no adverse reactions were observed.¹³⁶ On the basis of this experience a European multicentre randomized placebo-controlled trial of HA-1A in children with fulminant meningococcaemia had been recommended and is now in progress.^{137, 138}

Antibiotic therapy for meningitis

Over the last decade, newer cephalosporins have become available that are not only highly active against meningeal pathogens, but also achieve excellent bactericidal CSF concentrations with low toxicity. Changing patterns of bacterial resistance now challenge the use of the traditional combination of penicillin or ampicillin and chloramphenicol. Recommendation for therapy in childhood meningitis have been recently reviewed.^{139, 140}

In the neonatal period, coliforms and other Gram-negative bacilli, Group B streptococcus and *Listeria monocytogenes* are the most important pathogens. The use of triple therapy including an aminoglycoside is no longer recommended, due to the oto- and nephrotoxicity and poor CSF penetration. Ampicillin and cefotaxime are now favoured as first-line treatment, modifying the combination when sensitivities become known. Ceftriaxone is best avoided in the newborn as it is excreted in the bile and is more likely to alter gut flora than the other cephalosporins.

Between 1 and 3 months of age pathogens include both the neonatal organisms and those found in older children. In children over 3 months most cases of meningitis are due to *Neisseria meningitidis*, *S. pneumoniae* or *H. influenzae*, the latter predominating in children under 6 years. At least 15% of isolates of *H. influenzae* in the UK are resistant to ampicillin and up to 3% may also be resistant to chloramphenicol.¹⁴¹ Penicillin-resistant pneumococci and insensitive meningococci are still uncommon in the UK, but resistance is emerging as a cause for concern in Spain and South Africa.^{139, 142} Although chloramphenicol has been the mainstay of therapy for many years, the emergence of resistance, the potential for marrow toxicity and the need for monitoring drug levels due to variable metabolism are leading to unfavourable comparisons with the third generation cephalosporins, cefotaxime, ceftazidime and ceftriaxone. Cefuroxime, a second generation cephalosporin has been used extensively in the USA and Europe for treating meningitis, but there is evidence of delayed sterilization of the CSF and a higher incidence of auditory and neurological sequelae suggesting that it is less effective than cefotaxime or ceftriaxone.^{143, 144} Ceftazidime is less effective than cefotaxime against pneumococci and should be

reserved for the treatment of pseudomonal infection.

Although the mortality and long-term morbidity of patients treated by third generation cephalosporins is similar to conventional therapy, the safety, convenience and reliability of single agent therapy has led to the recommendations given in the table below. Ceftriaxone has yet to receive a UK licence. A duration of 7 days antibiotic for meningococcal infection and 10 days for *H. influenzae* and *S. pneumoniae* is recommended. Seven days of treatment may suffice but small trial numbers preclude firm recommendations.¹⁴⁵ Suspected cases of meningococcal septicaemia/meningitis should receive parenteral benzyl penicillin before transfer or admission to hospital, 1,200 mg for adults and children over 10 years, 600 mg for children aged 1–9 years and 300 mg for children under one year.¹⁴⁶ In the neonate, 14 days' treatment for Group B streptococcus and listeria, and at least 3 weeks for Gram-negative meningitis are recommended.

The advent of effective vaccines, and new therapeutic interventions to modulate the host inflammatory responses promises to improve the outlook for meningitis in the future.

Prevention – a new vaccine

H. influenzae is the commonest cause of meningitis, epiglottitis, cellulitis and septic arthritis in early childhood. The cumulative risk of invasive *H. influenzae* disease is 1:600 by the age of 5 years, with 39% of cases occurring under the age of one year, and the highest proportion of cases occurring between 4 and 12 months.^{147,148} Early vaccines prepared from the polyribosylribitol phosphate (PRP) capsule of *H. influenzae* alone showed inconsistent efficacy in widespread trials, particularly in children under 2 years. Although early Finnish studies showed 90% efficacy in children over 18 months,¹⁴⁹ several studies in the USA^{150,151} in children aged 18–59 months showed only

moderate efficacy (55–80%). Conjugation of specific proteins to PRP greatly improved the immunogenicity and four conjugate vaccines have been licensed in the USA and three in the UK. PRP-D is conjugated to diphtheria toxoid, PRP-CRM (Hb-OC) is conjugated to cross-reacting mutant diphtheria protein, PRP-OMP is conjugated to meningococcal outer membrane protein and PRP-T is conjugated to tetanus toxoid. A recent double-blind randomized controlled trial¹⁵² compared the immunogenicity and reactogenicity of the four conjugate vaccines when given to infants at 2, 4 and 6 months of age. Mean antibody levels after three injections of PRP-CRM (3.08 µg/ml) and PRP-T (3.64 µg/ml) were significantly higher than after PRP-OMP (1.14 µg/ml) or PRP-D (0.28 µg/ml). However, PRP-OMP produced clinically significant elevation in antibody titres after two doses (0.84 µg/ml) with only a small further increment in response to the third dose. PRP-T was the most immunogenic, able to stimulate levels above 1 µg/ml in 83% of individuals. In the UK,¹⁵³ safety and efficacy of the haemophilus type B oligosaccharide – CRM 197 (Hb-OC) conjugate has been confirmed using the 3,5,9 month schedule. Recently PRP-T has been evaluated in 107 infants using the 2,3,4 month schedule with concomitant triple vaccination. Results showed PRP-T to be highly immunogenic with 91% infants achieving levels over 1 µg/ml. At present *Haemophilus influenzae* type b (Hib) vaccine is given at a separate site to the triple vaccine. As Hib vaccines are conjugated to quite different proteins it is currently recommended that the full course should be of the same conjugate type. Studies in Finland suggest that titres of over 1 µg/ml correlate with long-term protection so that booster doses may not be necessary.¹⁵⁴ Vaccination started nationally in the UK in October 1992, beginning with the youngest, and all children under 5 years will be eligible. Children aged 2–12 months will receive three doses at monthly intervals and those of 13 months and over a single dose. More than 2 million doses of Hib vaccines have been

Table IX Recommended antibiotics for initial treatment of meningitis

Age group	Drug	Dose/kg/day
Neonates	Ampicillin and cefotaxime	150 mg (< 7 days), 200 mg (7–28 days)
		100 mg (< 7 days), 150–200 mg (> 7 days)
Infants 1–3 months	Ampicillin and cefotaxime	200 mg
		200 mg
Older infants and children	(1) Cefotaxime or	200 mg
	ceftriaxone	100 mg
	(2) Ampicillin and chloramphenicol	200 mg 75–100 mg

administered worldwide and there have been no reports of serious adverse reactions.¹⁵⁵ Household contacts of invasive *H. influenzae* disease under the age of 5 years should be vaccinated, and room contacts, if two or more cases occur in a playgroup or nursery within 120 days.¹⁴⁸

Given 95% vaccine uptake and an efficacy of 90%, Hib vaccination potentially could prevent 60 deaths and 1,170 cases of infection a year in the UK.¹⁵⁴

Although there is an effective vaccine against Group A and Group C meningococcal disease, unfortunately there is no effective vaccine against Group B disease which accounts for 69% of UK infections. Vaccination, as well as rifampicin prophylaxis should be offered to household contacts of Group A and C disease.

Child abuse

Family violence has increased markedly over the past 10 years and this trend has been well documented in the United States of America.¹⁵⁶ It is also well recognized in Britain with increased annual notifications to the NSPCC and increased numbers of children on Child Protection Registers.

Physical abuse may be recognized by specific indicators which may include the pattern of physical injuries, for example, multiple bruises of different ages in areas such as the trunk where accidental bruises are less likely to occur, finger marks across a child's face, bruising in the ears, particularly if bilateral, linear bruising, bite marks, cigarette and other burns, immersion-type scald injuries and evidence of fractures of differing ages. In addition it is important to assess the child's nutrition and growth, noting carefully any catch-up growth when away from the allegedly abusing home, his developmental status and any evidence of emotional disturbance. There is a strong inter-relationship between failure to thrive in young children, language delay and evidence of emotional disturbance.

Child sexual abuse

Physical and sexual abuse may co-exist in the same child and it has been estimated¹⁵⁷ that one in six physically abused and one in seven sexually abused children have been subjected to both. Nevertheless it is recognized that many sexually abused children may appear emotionally stable and seemingly unaffected.¹⁵⁸ They may also have no abnormal physical findings, making diagnosis difficult.

Child sexual abuse has only recently been recognized as a major child protection issue, considerably later than physical abuse which is on the whole both recognized and well managed. Increasing

numbers have been reported in this country over the last 7 or 8 years and in the USA for at least 10 years before this. There was initially a strong public denial of the existence of child sexual abuse except in the relatively rare instances of attempted rape by a stranger or serious mental illness on the part of the perpetrator, but studies of prevalence¹⁵⁹ indicate that there may be an overall rate of abuse (including non-contact incidence) of around one in ten of the population with incest occurring in a little above 1%. The estimated rate of contact abuse in male children¹⁶⁰ is around 2–5% and it appears that one boy is abused for every 2–4 girls. It seems likely however, that there is substantial under-reporting and detection of sexual abuse of boys.

The Inquiry into Child Abuse in Cleveland in 1987¹⁶¹ highlighted the difficulties in making a diagnosis of child sexual abuse, in particular referring to an inconsistent vocabulary used to describe physical signs associated with abuse and to major disagreements between branches of the medical profession regarding the significance of ano-genital signs. It appeared that doctors examining within a short period of each other either did not see or did not elicit the same clinical signs.¹⁶² Further, relatively little was known about the normal variation in the size and shape of female genitalia during the mid-childhood years nor about the pathophysiology and significance or otherwise of reflex anal dilatation and of laxity of the anal sphincter. Consequently, in December 1988 the Royal College of Physicians of London set up a working party whose remit was to agree terminology, describe the range of normal findings, advise on techniques of examination, produce evidence of the physical signs of child sexual abuse and assess their significance and produce suitable guidelines for the medical and legal professions.

The resulting report¹⁶³ weighed all the evidence carefully and the main conclusions were as follows:

- a. A substantial proportion of sexually abused children show no abnormal physical findings.
- b. Further data are required on the range and variation in normal appearances of pre-pubertal female genitalia.
- c. Variants of normal may closely mimic some signs resulting from abuse.
- d. The position and technique of examination greatly influence the findings, particularly with regard to the diameter of the hymenal orifice and also peri-anal signs.
- e. The hymenal orifice dimension is not a reliable indicator of abuse.
- f. There is a clear overlap between abused and non-abused populations with regard to physical signs which are consistent with and even suggestive of abuse. This is particularly so with regard to anal findings and reflex dilatation.
- g. Very few signs are diagnostic of abuse. These are

(in the absence of reasonable alternative explanation), a laceration or scar of the hymen, attenuation of the hymen with loss of hymenal tissue and a laceration or scar of the anal mucosa extending beyond the anal verge to the perianal skin. Pregnancy under 16 years of age and the presence of semen (on a girl) raise the question of abuse.

- h. The diagnosis of abuse is made or confirmed following a multidisciplinary investigation with full inter-agency cooperation. The single most important feature is a statement by the child. Detailed medical and forensic evidence may support this statement, as may a psychological assessment that the child has been abused or a confession by the perpetrator.

There is no doubt that sexual abuse is emotionally and psychologically damaging to the child and may have far-reaching effects. It is therefore important that all personnel to whom the child may present are receptive to the problem. Presentation may be by a statement by the child or by his/her carer or other friend, by physical symptoms, including vaginal discharge, inflammation, bleeding, sexually transmitted disease (rarely) or genital warts, by psychosomatic symptoms, by psychiatric symptoms or by school failure. The child may present to the general practitioner, paediatrician, child psychiatrist, dermatologist, gastroenterologist, gynaecologist, teacher and others.

It is of course of great importance not to misdiagnose abuse when a medical condition exists which may produce suggestive physical signs. The consequences to the child and family of a false positive diagnosis are potentially very serious. Such conditions include ano-genital lichen sclerosus,¹⁶⁴⁻¹⁶⁶ vulvar pemphigoid,¹⁶⁷ local accidental injury, myotonic dystrophy and other neuromuscular disorders leading to laxity of the anal sphincter, haemolytic-uraemic syndrome or other very severe illness in the child, Crohn's disease, local skin infections and chronic constipation.¹⁶⁸ It is therefore important to seek the opinion of the relevant expert.

Recent developments in this field include the recognition of increasing numbers of cases of sexual abuse in day care and in residential children's units.¹⁶⁹ Similarly ritualistic abuse has begun to be recognized¹⁷⁰ and is distinguished from other forms of sexual abuse by its bizarre and coercive elements. Physical and emotional abuse including sadism play an integral part and there may be both multiple perpetrators of both sexes and multiple victims.^{171,172}

When child sexual abuse occurs within the family it is extremely important to involve the family in the child protection plan. Where possible, as long as safety can be reasonably assured, the child should be allowed to remain at home. It is preferable for

the alleged abuser to leave the home if this can be arranged whilst investigations proceed.

Video recorded interviews with the child are now becoming acceptable within the legal system. Unfortunately the child is still required to be available at court to be questioned and many courts are establishing a video link with a private room where the child may sit separately from the court and accompanied by a female court officer. This avoids some of the stress associated with giving evidence in open court in close proximity to the alleged perpetrator. It is not, however, likely to be successful with young children to whom the whole procedure will still appear unnerving.

Munchausen by proxy

Many normal parents may exaggerate details of their child's illness in the hope of ensuring prompt or better medical help; or – through anxiety – perceive problems that are not apparent to others. Meadow, in 1977,¹⁷³ described the syndrome of Munchausen by proxy, in which parents fabricated both the history and signs of illness in their children, resulting in needless harmful investigations, hospital admissions and treatment.

The mother was invariably the source of the fraudulent history and the fabricator of signs which resolved in her absence. On occasions harmful substances were administered to the child. An extensive review¹⁷⁴ of 117 published cases indicates that the mother induced illness in 50% of the 72 cases where full details were known, with episodes occurring after hospital admission in 95% of cases. Hospitalization may increase the risk to the child and observation on an intensive care unit does not, surprisingly, prevent untoward events occurring.

Of the perpetrators, 98% were the biological mother and in only 1.5% of cases was paternal collusion suspected. The most common presenting features were bleeding (44%), seizures (42%), central nervous system depression (19%), apnoea (15%), diarrhoea (11%), vomiting (10%), fever (10%) and rash (9%). Mortality was 9% and limited to children under 3 years of age. The commonest cause of death was poisoning in 50%, followed by suffocation in 40%. There was a higher incidence of overt maternal Munchausen syndrome in the group that died than in the group as a whole.

With time, some children become involved in the deception. The mother's love is dependent on alleged illness, the children may corroborate and come to believe the maternal story, adopt the sick role and become chronic invalids and even 'Munchausen' themselves in later life.¹⁷⁵ Many of the children were suspected of having significant long-term psychological morbidity.

Many mothers have some paramedical background (27–52%). They appear devoted, unduly attentive, and reluctant to leave the child's side. Despite the severity of the illness and lack of progress towards diagnosis, the mother frequently seems less concerned than the medical staff.

Although many of the mothers have features of Munchausen syndrome, psychiatric assessment is often unrewarding.¹⁷⁶ In Rosenberg's series,¹⁷⁴ 12 mothers were suicidal, seven pre-disclosure. They may appear outwardly competent, but are often insecure with low self-esteem. The sick child brings the mother into a caring milieu. The child's 'illness' may be attention-seeking behaviour, a means of outwitting doctors and bringing emotional, material and social gain. Illness in the child may restore the marital relationship at the child's expense. One parent commented she liked the sympathy, 'I was somebody, I liked to feel considered by intelligent people', and seemed unaware of the dangers to her child.¹⁷⁷ The child's 'illness' may be a cry for help, the child's poisoning equating with self-poisoning.¹⁷⁸

Until recently, a surprisingly low incidence of other types of abuse had been associated with Munchausen by proxy syndrome. An undue number of siblings, however, were noted to have died in unusual circumstances, suggesting that they too may have been victims.¹⁷⁴ Bools¹⁷⁹ recently examined the co-morbidity associated with fabricated illness in a selected consecutive series of 56 children and 82 of their 103 siblings. A total of 64% of the index children and 39% of siblings had other episodes of fictitious illness and this figure rose to 80% in the subgroup of poisoned children. A substantial proportion had histories of failure to thrive, non-accidental injury, inappropriate medication, ingestion, or neglect. A total of 13 siblings had died and for 11 of these the reason was not medically conclusive.

The index children were subdivided by type of fabrication into four groups: smothering, poisoning, seizures, and miscellaneous. The 15 children who were smothered had repeated episodes over a period of 1–47 months, with a mean age at diagnosis of 15 months. Apnoea is a presenting feature in 15–30% of cases of Munchausen by proxy, but is also a common symptom in paediatrics. Severe life-threatening events that regularly occur only in the presence of one person are unusual and suggestive of Munchausen by proxy. Difficulties arise when a combination of manufactured, exaggerated or real symptoms coexist.^{180,181} In the miscellaneous group, fabrications included: haematemesis, haematuria, haemoptysis, urinary tract infections, glycosuria, pyrexia and a variety of food allergies and rashes.

A variety of noxious substances were administered, including common salt, salt plus a hypnotic,

lactulose, phenobarbitone, phenytoin, promethazine, 'Campden tablets' (sodium metabisulphite), amitriptyline, imipramine, lorazepam plus imipramine plus Milk of Magnesia, diazepam plus De-Nol plus aspirin. Two children died from the poisoning. Some siblings had been seen previously for ingestions, which with hindsight may not have been accidental. Other agents that have been used to generate illness are Ipecac, hydrocarbons,¹⁸² amylobarbitone with quinalbarbitone,^{178,183} insulin, phenformin, methaqualine, dihydrocodeine, frusemide and chlorthalidone,¹⁷⁸ Epsom salts¹⁸⁴ and metaldehyde.¹⁸⁵ One report documents that two siblings died, one from hypoglycaemic coma, the other after falling from a window.¹⁷⁸

An illustrative case is that of a 7 month old boy, the first child of married parents, who presented with a history of apnoea requiring resuscitation at home. There were no abnormal findings and no further episodes occurred over a 2 week period in hospital where all investigations proved negative. After discharge he relapsed and there followed a protracted and severe illness over several weeks with persistent vomiting, poor feeding, respiratory symptoms, acute gastrointestinal bleeding and recurrent status epilepticus. Repeated urine toxicology screens were negative. His mother stayed closely by him but it was noted that on two occasions the child's improvement followed the mother's going home for the night. The mother herself had a history of multiple hospital admissions which ceased following the birth of this child, who had already had a number of admissions with seemingly trivial complaints. After a further episode of vomiting followed by convulsions, toxicological analysis of the vomitus revealed metaldehyde and its metabolites. Subsequently, a bottle of proprietary molluscicide based on metaldehyde was found in the mother's room. Child protection proceedings were taken in respect of the child who has made good progress in foster care.¹⁸⁵

The diagnosis rests on a high index of suspicion. It is important to send samples of blood, urine and vomit at times when the child is symptomatic. If in doubt the parent and child should be separated. The importance of obtaining a detailed family history and corroborating details with the general practitioner, health visitor and other professionals involved with the family cannot be overemphasized. Meadow and co-workers¹⁸⁶ have compiled a list of warning signs with recommendations for dealing with suspected cases.

Confrontation with the mother may lead to admission, and to cessation of the abuse. Rarely, surveillance by video may be necessary to establish proof, for example, with suspected smothering. Worrying features identified by Meadow include:

1. abuse that has involved suffocation or poisoning;

- 2. abuse of a child under 5 years;
- 3. previous cot death, or other unexplained death of a sibling;
- 4. a lack of maternal insight, and absence of continuing support;
- 5. mothers with overt Munchausen syndrome themselves;
- 6. major adverse social factors such as drug dependency; and
- 7. persistence of fabrication even after confrontation.

All children in an index family are at risk of a variety of abuse and it is likely that professional involvement will be necessary until the children are adult, usually on a statutory basis.⁷

Advances in paediatric oncology

Childhood cancer is a rare disease. Around one child in 600 will develop cancer before the age of 15 years. However, unlike most adult cancers, the prognosis for the child with malignant disease has vastly improved over the last 20 years, and the majority of children with cancer survive 5 years from diagnosis, and well over 50% are cured.

The relative incidence of the different tumour types and the improvement in survival is shown in Table X. These data are taken from the national registry of childhood malignancy held by the Children's Cancer Research Group in Oxford.¹⁸⁷

The improvement in survival is mainly due to the use of chemotherapy, which alone can cure many childhood malignancies such as acute lymphoblastic leukaemia and non-Hodgkin's lymphoma. However, the improved survival is also due to the trend towards centralizing care for children with cancer. The majority of children with cancer are now treated at one of the regional paediatric

oncology centres. The Children's Cancer Study Group has shown¹⁸⁸ that children treated in such centres have a better outcome. Most children treated in paediatric oncology centres are entered into therapeutic studies, run by the Medical Research Council (MRC) or the United Kingdom Children's Cancer Study Group (UKCCSG), and this also has an effect on survival.¹⁸⁹

Survival from childhood cancer is not without cost, and now that many children can be expected to survive, the emphasis in treatment is changing from cure at any cost, to cure at the least cost to the child in terms of long-term consequences. The improvement in outlook for children with cancer as a result of more intensive chemotherapy regimens has only been possible because of the coincident improvement in supportive therapy, both in terms of blood product support, and the development of effective broad-spectrum antibiotics as many treatment regimens are extremely myelosuppressive. The development of haematopoietic growth factors may reduce even further the most common cause of treatment related morbidity, that is, sepsis, as a result of therapy-induced neutropenia.

The increasing interest in biological studies of malignant tissue has resulted in an improved understanding of the nature of cancer in children. Such studies may also provide information of prognostic value, which could be utilized in tailoring therapy.

Cytogenetics

A number of specific cytogenetic abnormalities associated with particular cancers have been described; some of the more common are shown in Table XI.¹⁹⁰ The cytogenetic result may sometimes be of use in diagnosis, for example, the presence of 11;22 translocation in an otherwise undifferen-

Table X Percentage 5 year survival

	Annual incidence (cases per 10 ⁶)	1971-1973	1977-1979	1983-1985
Acute lymphoblastic leukaemia	33.7	37	53	70
Acute non-lymphoblastic leukaemia	6.1	4	18	26
Hodgkin's disease	5.6	76	88	88
Non-Hodgkin's lymphoma	7.9	22	39	70
Medulloblastoma	6.1	24	36	42
Neuroblastoma	7.8	15	25	43
Wilms'	6.9	58	76	79
Osteosarcoma	2.6	17	28	54
Hepatoblastoma	0.8	8	17	40

Table XI Cytogenetic rearrangements in some paediatric malignancies

<i>Malignancy</i>	<i>Cytogenetic rearrangement</i>
Retinoblastoma	del(13) (q14)
Wilms' tumour	del(11) (p13);t(3,17)
Rhabdomyosarcoma	t(2;13) (q37;q14), t(2,11), 3p
Ewing's sarcoma	t(11;22) (q24;q12)
Peripheral neuroepithelioma	t(11;22) (q24;q12)
B cell non-Hodgkin's lymphoma	t(8;14) (q24;q32)
	t(2;8) (p13;q24)
	t(8;22) (q24;q11)
T cell non-Hodgkin's lymphoma	t(8;14) (q24;q11.2)
	t(14;14) (q11;q32)
	inv(14) (q11.2;q32.2)
Acute non-lymphoblastic leukaemia	
Acute myeloblastic leukaemia (M2)	t(8;21) (q22;q22)
Acute promyelocytic leukaemia (M3)	t(15;17) (q25;q22)
Acute lymphoblastic leukaemia	
Acute T cell leukaemia	t(11;14) (p13;q13)
Pre B cell leukaemia	t(1;19) (q23;p13.3)
Acute leukaemia (not defined)	t(4;11) (q21;q23)
Chronic myeloid leukaemia	t(9;22) (q34;q11)

tiated small round cell tumour in Ewing's tumour. Histological analysis of many childhood solid tumours show an embryonic-like picture, suggesting that an arrest in development has occurred. This results in the normal differentiating signals being overridden, leading to the proliferation and uncontrolled division of embryonic cells.

Tumour cells may express specific genes identifying the stage of development at which this arrest occurred. Since most tissues are fully differentiated at or soon after birth, the mutations responsible for tumorigenesis probably occur during embryogenesis. Once the cells are fully differentiated they are no longer available to the pool of potential tumour precursor cells. Tumour progression is characterized by further secondary genetic changes. Several embryonic tumours show familial aggregation, suggesting genetic predisposition. It is the analysis of tumours from these rare patients which has led in many cases to the pinpointing of the responsible mutation. The study of retinoblastoma in particular has been the prototype for the analysis of inherited cancer predisposition.

Genetics of retinoblastoma

In the early 1960s it was noted¹⁹¹ that some patients with retinoblastoma had other congenital abnormalities, dysmorphic features and mental retardation. This was shown to be associated with a deletion of part of the long arm of chromosome 13. The larger the deletion, the more severe the congenital abnormalities. With smaller deletions the only consequence was the development of retino-

blastoma. Subsequent work demonstrated that the development of retinoblastoma was associated with the deletion of a single gene. This was isolated by Friend, and independently by Fung.^{192,193} The precise function of the retinoblastoma gene is uncertain except that by inference it must be involved in control of normal retinal development.

Approximately 30% of cases of retinoblastoma have a family history of the disease. The condition is transmitted in an autosomal dominant fashion, that is, the inheritance of a single mutant gene is sufficient to produce the disease. It is the predisposition to tumour development that is inherited, and a further event must take place to result in the development of retinoblastoma. This is supported by the fact that, although all the retinal cells of an individual with familial retinoblastoma carry the defective gene, not all retinal cells develop into cancers. In addition there are a number of cases where the gene is inherited but retinoblastoma does not occur at all. Knudson¹⁹⁴ suggested that at least two genetic events were required for tumour initiation: the so-called 'two hit hypothesis'. The second always occurs after conception, as a result of an environmental or unknown agent. The first mutation can also occur post-conception, as in the sporadic non-familial cases, or pre-conception as in the familial cases. This explains why familial retinoblastoma occurs earlier (mean age of onset around 10 months) and tends to be bilateral or multifocal whereas the sporadic form has a mean age of onset of around 18 months and is usually unifocal.

Survivors of familial retinoblastoma have a

marked increased incidence of secondary malignant tumours, in particular osteosarcomas and soft tissue sarcomas. These are most commonly seen within the irradiated field but are also seen outside this, suggesting that the gene essential to normal retinal development also plays a role in bone and muscle development.

Oncogenes

Other biological studies include the study of oncogenes. The *N-myc* oncogene is a DNA sequence found in human neuroblastoma cell lines that shares homology with *v-myc* and *c-myc* oncogenes. Increased copies of *N-myc* (gene amplification) are seen in some neuroblastomas, and this appears to be of prognostic significance.¹⁹⁵ The presence of more than three copies is associated with a poor outcome. It is likely that further diagnostic advances may come from the careful study of biological material. Many of the current UKCCSG studies include the collection and storage of material for such studies, either now or in the future.

Advances in therapy

There have not been many new agents developed in the last 10 years, most of those in current use have been available for a lot longer. Advances in treatment have often involved changes in the timing and method of administration of each drug in order that the maximum therapeutic benefit can be obtained with the minimum of side effects.

Acute lymphoblastic leukaemia (ALL)

Figure 1 shows the survival for children with ALL treated at the Sheffield Children's Hospital for three successive quinquennia. The improvement in survival is largely due to the use of increasingly intensive chemotherapy regimens conducted by the MRC: the United Kingdom Acute Lymphoblastic Leukaemia (UKALL) studies.¹⁹⁶

The aim of the initial treatment is to achieve remission, and most current recent regimens have used combinations of vincristine, asparaginase, prednisolone and daunorubicin. Over 95% of children achieve remission with such treatment. Improved supportive care has resulted in a reduction of deaths during induction therapy.

Multivariate analysis of the UKALL studies has shown that the following features have independent prognostic value: initial white cell count above 100,000/mm,¹⁸⁹ age under 1 year, immunophenotype mature B cell, and specific karyotypic changes (for example, the presence of the Philadelphia chromosome, 4;11 translocation). The L2 subtype, FAB morphology, hyperdiploidy and T cell immunophenotype are of borderline prognostic significance in multifactorial analysis.

Children with mature B cell leukaemia which less than 20 years ago had a dismal prognosis no longer receive standard ALL regimens, but are treated in a similar way to children with bulky B cell non-Hodgkin's lymphoma. This has resulted in a marked improvement in their survival.¹⁹⁷

It is not clear whether all children with ALL require intensive chemotherapy once remission has been achieved. It would seem logical that

Figure 1 Survival for children diagnosed 1972–1986 with acute lymphoblastic leukaemia. – = 1972–1976 (*n* = 81); ..... = 1977–1981 (*n* = 76); - - - = 1982–1986 (*n* = 75).

leukaemic cell resistance might be overcome if additional agents were given after remission has been achieved, and this is the basis for the recent MRC trial UKALL X.¹⁹⁸ Using this approach the German BFM group¹⁹⁹ have shown improved survival especially for 'high-risk' patients.

Prior to the addition of central nervous system (CNS) directed therapy up to 60% of children with ALL relapsed in the central nervous system. Cranial irradiation and intrathecal methotrexate injections have reduced the incidence of CNS relapse to less than 10%.^{200, 201} Radiation doses have been reduced in subsequent UKALL studies from 24 Gray to 18 Gray. Concern about the effect of irradiation on endocrine function²⁰² and on intellectual development²⁰³ have led to attempts to replace cranial irradiation with chemotherapy alone.

In UKALL XI the addition of repeated courses of high-dose methotrexate with folinic acid rescue is under study to test whether it will reduce the proportion of patients relapsing and whether it will improve the control of CNS disease, and possibly result in fewer long-term intellectual and endocrine effects.

Continuation therapy

Once complete remission has been obtained additional 'maintenance' or continuation therapy is required. Early studies showed that without additional therapy most patients achieving remission relapsed within a few months, and that the time of unmaintained remission varied with the intensity and duration of the preceding treatment. To be effective in preventing relapse continuation therapy must provide continuing cytoreduction and suppress leukaemic growth without permitting the emergence of a drug-resistant clone. The duration of continuation treatment has been gradually reduced as a result of randomized studies which showed no advantage for more prolonged therapy.²⁰⁴

The combination of 6-mercaptopurine and methotrexate administered continuously has been widely used and is the principal element in most continuation therapy regimens. The UKALL studies also include pulses of vincristine and prednisolone.

Drug dosage is an important factor in continuation therapy. Patients who receive therapy on a continuing schedule rather than an interrupted schedule have longer remission duration.²⁰⁵ Paradoxically children who are very sensitive to mercaptopurine with resulting neutropenia at low dosage have a better outlook when compared with children able to tolerate higher doses of this drug. This effect is linked to the variable metabolism of mercaptopurine.

It has been shown that boys tolerate mercaptopurine better than girls.²⁰⁶ This may in part be due to genetic differences in the levels of enzymes involved in the metabolism of mercaptopurine to the active cytotoxic metabolites: thioguanine nucleotides.²⁰⁷ This may be related to the still unexplained difference in prognosis between sexes.

Bone marrow transplantation in ALL

Because of the severe long-term consequences, with graft versus host disease, endocrinopathies and growth failure, bone marrow transplantation is only considered for patients with ALL in second or subsequent remissions. The use of bone marrow transplantation for ALL in first remission is controversial, and should be restricted to those with very poor prognostic features, for example, young infants, particularly those with high white cell counts, chromosomal abnormalities such as t(9;22) or for those patients who have a slow response to initial induction therapy.

Elective high dose therapy with allogeneic bone marrow transplantation or autologous bone marrow rescue are currently under investigation for such patients.^{208, 209}

Neuroblastoma

Neuroblastoma arises from fetal neuroblasts which normally migrate from the neural crest to the sympathetic ganglia and adrenal gland. Although the overall survival for children with neuroblastoma has improved over the last 20 years this has been mainly because of improved management of children with early stage disease, that is, Stage 1, 2 and 4S. Children with widespread disease at presentation continue to have a poor outlook, despite intensification of therapy. Stage at presentation is an important prognostic factor as is age.²¹⁰

Biological factors associated with outcome have recently been identified, the most important include DNA ploidy and *N-myc* amplification. The levels of serum markers such as neurone-specific enolase and ferritin are also of prognostic significance. Early stage disease and infants appear to have lower levels of *N-myc* amplification, and to be more likely to have hyperdiploid tumours compared to older children and children with more extensive disease. It seems likely that there are two types of neuroblastoma, with differing prognosis, and that most of the improvement in survival has come in the good prognosis group.

In an attempt to improve the poor outlook for children with stage 4 disease, the European Neuroblastoma Group (ENSG) has over recent years carried out a series of studies of increasingly intensive chemotherapy. The results of a pilot study of children with stage 4 disease treated using a high

dose rapidly scheduled regimen (with chemotherapy given every 10 days, regardless of neutropenia) are encouraging with more patients achieving remission than on previous protocols.²¹¹

The current ENSG stage 4 study (ENSG 5) is a randomized trial comparing this high dose rapid schedule regimen with a conventional schedule, followed by further high dose chemotherapy and autologous bone marrow rescue.

Targeted therapy

Meta-iodobenzylguanidine (MIBG) is a substance taken up specifically by neural crest tissue, particularly neural crest tumours, such as phaeochromocytoma and neuroblastoma.²¹² It is possible to image and also treat such tumours²¹³ by radiolabelling MIBG with an iodine isotope, usually ¹³¹I or ¹²³I. Although there have been a number of studies describing the use of MIBG in treating relapsed patients,²¹⁴ because of problems in determining the correct dose of radiation to deliver to the tumour this therapeutic strategy has not been more widely used.

cis-Retinoic acid

cis-Retinoic acid has been shown to produce ganglionic differentiation in undifferentiated neuroblastoma cell lines.¹²⁵ The role of *cis*-retinoic acid in patients with minimal residual disease is currently being evaluated by the ENSG in a placebo-controlled double-blind study where children with incomplete or good partial remission following treatment for stage 3 or 4 disease are given *cis*-retinoic acid for up to 4 years.²¹⁶

Screening for neuroblastoma

The observation that younger children with neuroblastoma have a better outlook coupled with the fact that the majority of neuroblastomas secrete

catecholamines, the metabolites of which can be detected in urine has led many groups, most notably the Japanese to adopt screening programmes in an attempt to reduce mortality.

Sawada²¹⁷ started screening projects in the early 1970s. Following initial promising results the Japanese government funded screening for all 6 month old babies in Japan. The preliminary results do suggest that neuroblastoma can be detected at an early stage, and that those so detected appear to have a better prognosis than previously. However, a major problem appears to be that screening is detecting tumours that would otherwise have spontaneously regressed, as the incidence of neuroblastoma has increased substantially in screened populations. There have also been a small number of cases negative on screening who have developed the disease in later childhood.

A number of other groups are currently undertaking screening programmes, including a number of regions in the United Kingdom.²¹⁸ It will be at least 5 years before the results of these studies are available.

Cytokines

Following the initial intense interest in the use of interferon as an anti-cancer agent (which never fulfilled the anticipated potential) there has been an explosion in the development of other cytokines and it looks as if these may be a totally new class of therapeutic agent. With advances in genetic engineering it is now possible to produce large amounts of pure cytokines including interferon. Cytokines are polypeptides which are involved in the regulation of growing cells, or in the support and proliferation of precursor cells. Table XII shows some of more than 30 substances currently recognized as cytokines.

There have been a large number of studies carried out using cytokines. Cytokines can be used as supportive, cytotoxic or immunomodulatory

Table XII Cytokines in clinical use

Cytokine	Clinical application
Interferons IFN- α , β and γ	IFN- α : chronic leukaemias, hepatitis B
Interleukins IL-1 to 9	IL-2: refractory cancer (immunomodulatory function)
Haemopoietic growth factors Erythropoietin Granulocyte colony stimulating factor (GM-CSF) Granulocyte colony stimulating factor (G-CSF) Macrophage colony stimulating factor (M-CSF)	Anaemia (chronic renal failure) Congenital and chemotherapy induced neutropenia, aplastic anaemia and AIDS
Tumour necrosis factors TNF- α and β	Refractory cancer

factors. In general, in childhood malignancy, studies have largely looked at the use of supportive factors such as G-CSF and GM-CSF. Studies have been carried out in children undergoing bone marrow grafts and a variety of chemotherapy regimens.

The French Neuroblastoma Group have reported on the effects of GM-CSF in a double blind randomized study following either the first or second of two high-dose therapy autograft procedures. Following the first regimen children who received GM-CSF had a significantly shorter median time to leucocyte recovery with a significant reduction in the need for antibiotics. This effect was not seen, however, after the second regimen which included total body irradiation in addition to chemotherapy, presumably reflecting the more intensive regimen, and the degree of previous treatment.²¹⁹

The UKCCSG is currently conducting a randomized study of subcutaneous GM-CSF to assess whether its routine use in myelosuppressive chemotherapy regimens will reduce the incidence of neutropenia-related infection.

Studies in some adult malignancies such as hairy cell leukaemia and melanoma have shown impressive response rates using biological response modifiers such as interferon and tumour necrosis factor. A subgroup of normal lymphocytes, lymphokine activated killing cells (LAK cells) have been shown to kill cancer cells *in vivo*. There is increasing evidence that these need various cytokines to become active, and it is possible that this natural killing ability can be modified by the administration of cytokines such as interleukin II and interferon. The use of cytokines other than growth factors has not as yet been studied to any great extent in childhood malignancy but interest is growing.²²⁰

Late effects

As survival improves the importance of ensuring that this has been achieved at least possible cost to the patient in terms of late effects increases. It has been estimated that by the year 2000, one adult in 1,000 will be a survivor of childhood malignancy. With advances in chemotherapy, radiotherapy has been dropped from many regimens, with a resulting lessening in the severe toxicity this modality of treatment can have on growing tissues.

In view of the fact that many late complications may not manifest themselves for several years it is of vital importance that paediatric oncologists continue to monitor their patients for the development of late effects. This is emphasized by the accumulating evidence of late cardiotoxicity developing in patients treated with anthracyclines such as doxorubicin.^{221,222}

A number of analogues of chemotherapeutic agents have been developed in recent years, in the hope that these will provide effective treatment with fewer side effects than the drug they have been designed to replace. Whilst this is true of certain drugs such as carboplatin which is undoubtedly less nephrotoxic than its analogue cisplatin, other drugs such as ifosfamide whilst having similar or better antitumour effects to cyclophosphamide have been shown with increasing usage to have potentially serious long-term consequences.²²³

The advances in the management of children with cancer have resulted in many more children surviving. Many of the current survivors have significant late effects of therapy. Current treatment regimens are designed with the aim of minimizing these effects. The future lies with their elimination, so that 'cure at any price' becomes 'cure at no cost'.

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