
Chlamydia trachomatis is a major cause of sexually-transmitted disease and, as a consequence, poses a considerable threat of conjunctival and respiratory tract infection to the neonate. However, despite the medical and biological importance of chlamydiae, progress in the study of their pathogenesis, biology and antigenic composition has been limited by difficulties in culturing and purifying these fastidious parasites. Therefore, adopting an alternative strategy, DNA was purified from C trachomatis (serovar L2), partially digested with restriction enzyme Bam HI, ligated into the plasmid vector pUC13 and a genomic library was constructed by transformation of Escherichia coli. Bacterial colonies containing recombinant plasmids were subsequently screened with a monoclonal antibody which recognises an epitope shared by all members of the genus Chlamydia and which is located in the lipo-oligosaccharide present in the outer membrane of the parasite. Six recombinant bacterial colonies which reacted positively with the monoclonal antibody were identified. All possessed a common Bam HI fragment of 6-9 kilobase pairs (kbp). with the transforming activity to produce monoclonal antibody reactivity being excluded from 1-7 and 0-8 kbp PstI-Bam HI and Bam HI-EcoRI fragments lying within this stretch of DNA. Analysis of lipo-oligosaccharide from the recombinant E coli by polyacrylamide gel electrophoresis showed all six to possess a more rapidly migrating component which was reactive with the monoclonal antibody.

The cloning of this chlamydial component and the characterisation of the DNA and gene products encoded by it provides a potentially valuable tool for the study of the pathogenesis and also the diagnosis of this pathogen.

Normal placental transfer in the human. MD Bain, DK Copas, MJ Landon, and TE Stacey (Harrow and London).

Placental insufficiency, implying inadequate transfer functions, is frequently incriminated as contributing to perinatal morbidity and mortality. Inadequate transfer of what, and by how much, is unclear.

We have measured placental transfer in normal human placenta at term, of four substances with molecular weight range 182-5000, namely, mannitol, lactulose, Cr EDTA and inulin. This range covers many of the important fetal nutrients. A steady state maternal profile was achieved by a bolus and continuous infusion of a solution of these markers. As they are inert, and solely and wholly excreted by the kidney, net placental transfer before delivery equals the total subsequent neonatal urinary excretion.

Placental transfer, expressed as a clearance, was derived by dividing the net transfer by the time-averaged transplacental concentration gradient.

Growth in childhood and mortality in adult life. DJP Barker, CM Law, and C Osmond (Southampton).

There is increasing evidence that influences acting early in life are major risk factors for stroke, ischaemic heart disease and chronic bronchitis. Part of this evidence comes from epidemiological observations of striking geographical relations between current mortality from these diseases in England and Wales and indices of maternal and child health in the early years of this century. Relationships between adult diseases and childhood influences can be explored through height, since this is largely determined by growth in early childhood. Using data from the three national birth cohorts we have shown that differences in average heights between the counties of England and Wales have persisted over 50 years. There is a strong inverse relation between average height in the counties and mortality from the three diseases. The distribution of stroke also correlates with geographical differences in mean blood pressures of mothers and their 10 year old children. There is a strong positive
relation between height and cancer of the breast, ovary and prostate which suggests that promotion of child growth has disadvantages as well as benefits.

We have also analysed place of birth of two million people who died in Britain during 1969–72. The risk of dying from stroke, ischaemic heart disease and chronic bronchitis is related to place of birth within Britain, independently of subsequent migration. Differences in child growth may predict future differences in adult disease.

**Adults born with oesophageal atresia and tracheo-oesophageal fistula.** P Chetcuti, N Myers, S Beasley, and P Phelan (Melbourne, Australia).

One hundred and twenty five of 145 survivors born with oesophageal atresia and tracheo-oesophageal fistula prior to 1969 were reviewed to evaluate the outcome in an adult population. All case notes were studied, patients interviewed and examined and detailed lung function performed. The majority are comparable to their peers.

Over half had symptoms referable to the upper gastrointestinal tract and a third complained of wheezing in the 12 months prior to review, but in the majority the symptoms were occasional. Hospitalisation was required in only three patients, for pneumonia. Lung function data showed evidence of mild obstructive airways disease with a mean % predicted forced expiratory volume in 1 second of 85-06.

The eventual outcome is encouraging. Knowledge of this will improve counselling of parents of children with the condition who often require frequent and prolonged hospital admissions after initial surgery.

**When is a cluster a cluster? When it is next to a Nuclear Power Station??** AW Craft, S Openshaw, M Charlton, and J Birch (Newcastle upon Tyne and Manchester).

Unusual geographical and temporal aggregations of leukaemia have been described for over 60 years. Many techniques have been developed to determine whether clusters are anything other than chance but the matter is unresolved. Much recent work has centred on the nuclear industry and there have been several reports of clusters of leukaemia around such installations although most have started with this as an a priori hypothesis. A method has been developed to look dispassionately at a population independently of any preconceived ideas as to causation and disregarding arbitrary administrative boundaries. Registration data for 1968–85 from the Newcastle and Manchester children’s cancer registries, a total population of almost 9 million, have been analysed. A series of overlapping circles measuring 1–25 km have been constructed which totally cover the whole of the study area with 812 993 circles. The rate of cancer for each circle is retrieved using postcode registration data and 1981 census population information. The significance of each circle is determined using a Monte Carlo simulation technique and circles surviving a level of p<0-002 are drawn. If the distribution were Poisson then 173 circles would be expected to survive and be scattered all over the map. Wilms’ tumour, which has been thought to be randomly distributed, fits this pattern. However, that for acute leukaemia, both myeloid and lymphoblastic (ALL) and non-Hodgkins lymphoma are not random and dramatic clusters appear on the map, most being nowhere near a nuclear installation. For ALL 1972 circles survive at p<0-002. This technique will define a cluster. When applied to data from the whole of the United Kingdom new insights will be provided into the aetiology of childhood cancer. It can also be applied to any rare disease or condition. Neural tube defects are currently being examined.


Abnormal red cell membrane Na transport, manifested by high intracellular Na concentration (IcNa), low Na efflux rate constant (ERC) and decreased numbers of Na-K ATPase pump sites (Bmax) have been previously reported in children with EH. It is unclear whether these abnormalities are caused by hypertension, are a cause of hypertension or are just markers for hypertension. Using the same methods 28 index hypertensive children and their families were studied. In 15 families one or both parents had EH or a strong positive family history of EH. In 13 families neither parent had EH nor had a positive family history. Significant differences were found between the children with a positive family history of EH compared with those without. Mean (SD): IcNa (mMol/l cells) 8-19 (2-18); 6-41 (0-98) p<0-001; ERC 0-4873 (0-1379); 0-5831 (0-1104) p<0-01; BMax (mMol/l cells) 7-96 (1-71); 9-56 (1-7) p<0-001. There was a strong correlation between children and their parents in terms of IcNa, r=0-60 p<0-001; ERC r=0-51, p<0-001 and BMax r=0-42, p<0-001. No correlation was found between IcNa, ERC or BMax and age, body mass index, urinary Na excretion, plasma renin activity and systolic or diastolic blood pressure standard deviation scores.
Our data suggest that abnormal red cell membrane Na transport has a familial component and although not caused by the hypertension it may be the earliest pathophysiological step in its development, perhaps allowing the identification of children at risk of EH.

**Improving prognosis for cystic fibrosis in the United Kingdom 1977-85.** JA Dodge (on behalf of the BPA Working Party on Cystic Fibrosis).

This study attempted to identify all patients with cystic fibrosis alive in the United Kingdom at any time between 1977 and September 1985. A total of 6220 subjects were entered into the database. Age-specific mortality rates were calculated for the two periods.

Considerable improvement in prognosis has occurred during the period under study, particularly in the under 5 years age group. Comparative data also showed that survival is better in patients managed in large cystic fibrosis centres than in small local clinics.

### Current survival: large v small clinics

<table>
<thead>
<tr>
<th>Survival to age (years)</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Large</td>
<td>Small</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>1</td>
<td>97.2%</td>
<td>96.1%</td>
<td>94.8%</td>
<td>95.3%</td>
</tr>
<tr>
<td>5</td>
<td>94.7%</td>
<td>92.0%</td>
<td>91.8%</td>
<td>89.9%</td>
</tr>
<tr>
<td>10</td>
<td>87.2%</td>
<td>85.5%</td>
<td>83.5%</td>
<td>79.6%</td>
</tr>
<tr>
<td>15</td>
<td>77.5%</td>
<td>70.8%</td>
<td>69.0%</td>
<td>65.8%</td>
</tr>
<tr>
<td>20</td>
<td>64.5%</td>
<td>60.0%</td>
<td>49.7%</td>
<td>48.2%</td>
</tr>
<tr>
<td>80%</td>
<td>14 years</td>
<td>11 years</td>
<td>12 years</td>
<td>10 years</td>
</tr>
<tr>
<td>50%</td>
<td>25 years</td>
<td>20 years</td>
<td>23 years</td>
<td>20 years</td>
</tr>
<tr>
<td>Age standardised mortality/1000/year</td>
<td>19.9</td>
<td>29.4</td>
<td>23.1</td>
<td>32.4</td>
</tr>
</tbody>
</table>

Regardless of any future improvements in treatment, numbers of adult patients with cystic fibrosis will inevitably increase in the United Kingdom during the next decade, highlighting the need for appropriate medical services.

### Incidence of and risk factors for cerebral palsy in two national cohort studies.** A Emond, J Golding, and G Peckham (Bristol and London).

It is widely assumed that the incidence of cerebral palsy has been reduced by improved perinatal care. This hypothesis has been tested using the 1958 British Perinatal Mortality Survey and the 1970 British Births Survey. In spite of a reduction in the stillbirth and neonatal mortality rates, the incidence of cerebral palsy remained constant at 2.5/1000 births. The prevalence at 10 years was higher in the 1970 cohort in which all children with cerebral palsy survived, whereas in the 1958 cohort 22% of cases of cerebral palsy (diagnosed between 1 month and 7 years of age) died before the age of 10.

A case control study, matching for mother’s social class, age, parity and marital status, and the infant’s sex, gestation and birthweight, was undertaken for all cases of cerebral palsy. (40 from 1958, 41 from 1970). Comparison of cases and controls showed no consistent differences with respect to social and environmental factors, history of pregnancy, labour or delivery. Birth weight and gestation did not have a significant effect on the risk of cerebral palsy. Major differences were apparent in the frequency of respiratory and neurological symptoms in the neonatal period.

These prospective data derived from two whole populations of births suggest that the majority of cases of cerebral palsy are not associated with an abnormal pregnancy, labour or delivery, and confirm that neonatal neurological symptoms are good predictors of subsequent cerebral palsy.

### Parental smoking habits and wheezing and bronchitis in the child.** A Evans (Bristol).

Many authors have found associations between early bronchitis and/or wheezing episodes in the child and passive smoking, but few have attempted to ascertain at what age the child is most susceptible. Data to examine this were derived from the longitudinal study of the singleton children born to 17 000 women delivering in the United Kingdom during one week in April, 1970, who were followed up at the ages of 5 and 10. Smoking history of the mother was obtained in 1970, and for both parents in 1975 and 1980. Comparisons were made between children of four groups of mothers: those who smoked throughout pregnancy, those who gave up smoking during pregnancy, those who didn’t smoke during pregnancy but whose parents smoked during the child’s first 5 years, and households where neither parent smoked during the first 5 years of the child’s life. After adjusting for social and environmental factors associated with each aspect of smoking, wheezing and bronchitis in the child up to the ages of 5 and 10 years were both significantly more likely amongst the children of mothers who smoked during pregnancy. Apart from this, children whose mothers stopped smoking during pregnancy and those who were unexposed during pregnancy but exposed in the first 5 years did not differ in symptomatology from those whose parents were non-smokers throughout. The results would support a hypothesis of permanent damage to the fetal lungs due to smoking in the early stages of pregnancy.
Diagnosis of X linkage in sporadic cases of severe combined immune deficiency. J Goodship, S Malcolm, Y Lung Lau, ME Pembrey, and R Levinsky (London).

Severe combined immunodeficiency (SCID) is a syndrome in which affected infants lack cellular and humoral immunity and die from overwhelming infection if bone marrow transplantation is not performed. With the exception of inherited deficiencies of adenosine deaminase and purine nucleoside phosphorylase the autosomal and X-linked forms cannot be distinguished clinically. Females carrying the X-linked form are immunologically normal.

The methylation pattern at the 5' end of the PGK gene is different and constant between active and inactive X chromosomes. In females heterozygous for the PGK polymorphism it is possible to distinguish between a population of cells with random X inactivation and a population with non-random X inactivation using methylation sensitive restriction endonucleases.

We have previously shown that obligate carriers of X-linked SCID have a non-random population of T cells. We have now investigated women who have only one affected male child and where there is no previous family history of the disorder to see if they are carrying the X-linked form.

As the PGK gene is closely linked to the disease locus we can distinguish which polymorphic allele represents the inactive—that is, affected X chromosome—by its methylation. We therefore have a novel method of establishing linkage phase in women whom we show to be carriers without tracking alleles through the family. This is extremely useful when the woman may be a new mutation and she does not have surviving sons to establish phase. It increases the number of women who can be offered early prenatal diagnosis.

Improved outcome following natural surfactant treatment in severe respiratory distress syndrome. HL Halliday, G McClure, MMcC Reid, and B Robertson (on behalf of the Collaborative European Multicentre Study Group).

In a small randomised controlled trial of natural porcine surfactant (Curosurf) replacement in babies with severe respiratory distress syndrome (on mechanical ventilation, >60% oxygen, less than 15 hours old) we have shown a significant reduction in the complications of pneumothorax and intraventricular haemorrhage in treated babies. In an extended European Multicentre Study, mortality was also reduced (table).

<table>
<thead>
<tr>
<th></th>
<th>Treated (n=77)</th>
<th>Control (n=69)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation (weeks)</td>
<td>28.8</td>
<td>28.4</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1248</td>
<td>1333</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen need at entry (%)</td>
<td>80</td>
<td>80</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>24 (31)</td>
<td>35 (51)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pneumothorax (%)</td>
<td>14 (18)</td>
<td>24 (35)</td>
<td>0.05</td>
</tr>
<tr>
<td>Alive without BPD (%)</td>
<td>42 (55)</td>
<td>18 (26)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The 95% confidence limits for the reduction in mortality (4 to 36%) and survival without bronchopulmonary dysplasia (BDP) (18 to 40%) demonstrate a very important effect of this surfactant in the treatment of severe respiratory distress syndrome.

In the eight collaborating European Centres surfactant is now administered to all babies with severe respiratory distress syndrome. Is it now unethical for all units not to treat these babies provided supplies of surfactant allow?


A major function of the colon is the conservation of salt and water and we have previously shown that in the human infant it plays a major homoeostatic role. Colitis may therefore assume greater importance especially in diarrhoeal diseases than in later life. The only previous studies of the mechanisms involved in infants have been in vivo where electrical gradients influence ionic movements. We have carried out a detailed study of transport in normal and inflamed isolated human infant colon using an Ussing chamber and a voltage clamp procedure. Stripped colonic mucosa normal (n=6 pairs) and inflamed (n=5 pairs) was mounted and bathed in Krebs solution. Under short-circuit conditions Na+ (3-45 (1-53) μmol/hr/cm² mean (SD)) and Cl⁻ (0-63 (3-61)) were absorbed and a residual ion flux consistent with HCO₃⁻ secretion approximated Cl⁻ absorption. Short circuit current (Isc) (3-8 (0-28)) was very similar to net Na⁺ movement and was markedly reduced by mucosal 10⁻⁴ amiloride (0-61 (0-7) p<0.01). Inflamed mucosa generated a lower potential difference (2-44 (0-1) v 6-5 (1-0) mV p<0.01) ISc (1-62 (0-8) v 3-87 (0-5) p<0.02) and was of lower resistance (67-2 (12) v 104 (10) p<0.01).

Na⁺ was secreted and anion exchange reversed due to large increases of serosal to mucosal fluxes (Na⁺...
5-63 (0-1) to 15-7 (1-2) Cl\(^-\) 13-86 (1-64) to 20-9 (3) with no change in mucosal to serosal fluxes. These data show that Na\(^+\) is absorbed electrogenically and Cl\(^-\) electroneutrally in exchange for HCO\(_3\)^-. In the presence of inflammation the electrical and flux changes suggest a decrease in resistance of shunt pathways which dissipate absorbed Na\(^+\) and Cl\(^-\). Inflammation of the infant colon therefore seriously impairs its ability to conserve salt and water, and would thus make an important contribution to a dehydrating diarrhoeal disease.

Acoustic emissions and automated BAER in the newborn. C Kennedy, P Evans, L Kimm, S Lenton, and R Thornton (Southampton).

Following presentation of an auditory stimulus via an ear probe, low intensity echoes from the cochlea—acoustic emissions—may be recorded by a receiver in the same probe and analysed using a programmable otoacoustic emissions measurement system (POEMS). In adults, acoustic emissions are always lost early in the course of hearing loss. In order to compare POEMS and ALGOTEK—an automated pass/fail test based on brain stem auditory evoked responses (BAER)—both tests are being used in addition to conventional BAER to screen newborns. SCBU, other high-risk, and low-risk groups are being tested. All newborns who ‘fail’ one of these tests and a random sample of those who pass are retested at 3 months of age and subsequently. In 70 newborns tested to date, acoustic emission was not recordable in one or both ears at or below 61 dB in five, nor at or below 51 dB in a further five. BAER were not recordable at or below 60 dB in 1 nor at or below 45 dB in a further five. Two newborns have failed on ALGOTEK. Further results including follow up data will be presented. Our results to date suggest a false-positive rate at 60 dB not exceeding 7% for any of these three tests. Validation of ALGOTEK as a detector of auditory impairment is part of the present study. However previous studies suggest that false-negatives for deafness do not occur with POEMS. POEMS requires only the insertion of an ear probe: no electrodes are needed and testing time is consequently short. POEMS may prove superior to currently available neonatal screening techniques for auditory impairment.

Electromagnetic stimulation of the motor cortex: a simple and painless technique to measure objectively corticospinal tract function in newborn babies and children. THHG Koh and JAE Eyre (Newcastle upon Tyne).

Previously there has been no objective measure of corticospinal tract function in young children and newborn infants, resulting in the delayed diagnosis of cerebral palsy. Painless non-invasive electromagnetic stimulation of the motor cortex (EMSMC) is now possible; the latency from EMSMC to the evoked muscle action potential (MAP) has been shown to be a sensitive measure of corticospinal tract function in adults.

Following an assessment of its safety in an animal model, we have used EMSMC to study the maturation of the corticospinal tract and to assess its sensitivity to detect upper motor neuron lesions (UMNL) in children. One hundred and forty two normal subjects (2 weeks’ gestation to 50 years), 17 children with UMNLs (12 months–12 years) and seven comatose children with an acuteencephalopathy (4–16 years) at risk of sustaining an UMNL were studied.

For EMSMC a pulsed magnetic field ≤1-9 Tesla was used and MAPs recorded from abductor digit minimini. For each subject the ratio, height (m)/ latency from EMSMC to MAP(s), an index of conduction velocity (V\(_1\)) in the corticospinal tract was calculated.

MAPs were evoked in all the normal subjects including preterm infants; V\(_1\) increased with age from 10-5 m/s at 32 weeks’ gestation until adult values (79 m/s) were achieved at 10–14 years. Ten of the 17 children with UMNLs had hemiplegia: on the affected side MAPs were absent in eight and abnormal in two; MAPs were all normal on the unaffected side. In the seven with bilateral UMNLs, MAPs were bilaterally absent in five, unilaterally absent in two. In the seven comatose children: all three with bilaterally absent MAPs died, two with unilaterally absent MAPs survived with hemiplegia on that side and two with bilaterally normal MAPs survived without handicap.

In conclusion EMSMC is a simple painless technique to assess the maturity and integrity of corticospinal tract function in young children. We are currently assessing its potential for the early detection of cerebral palsy in a prospective study.

We thank the MRC and Newcastle Health Authority.

Antenatal diagnosis of fetal malformation—a population study. MJ Lewins (Hull).

To assess the success of a routine screening programme for structural fetal abnormality and to review the management of identified cases, all pregnancies within the population of Hull and East Yorkshire ending in 1986 were studied. From a total population of 500 000, 8232 pregnancies were included: 811 pregnancies ended spontaneously in the first trimester.
Major structural fetal abnormality was ultimately found to be present in 87 pregnancies, 40 of which were diagnosed antenatally. Details of the type of abnormality, methods of diagnosis and management of the affected fetus and newborn will be presented.

Of the 795 medical terminations of pregnancy performed 22 were for identified fetal abnormality. All but one of these were for fetuses with either neural tube defects or major chromosomal abnormalities. In cases where a malformed fetus was identified and pregnancy continued a multidisciplinary counselling service was offered.

It was concluded that: (1) current methods of routine antenatal diagnosis identified less than 50% of major structural fetal abnormalities; (2) few fetuses with surgically correctable malformations were aborted; (3) the scope for antenatal counselling of parents of malformed children is limited but nevertheless potentially important.

**Alteration in a calmodulin binding protein in cystic fibrosis exocrine glands.** MA McPherson, RL Dormer, DK Shori, NA Bradbury, and MC Goodchild (Cardiff).

Although DNA probes closely linked to the cystic fibrosis locus have been discovered, the biochemical basis of the disease is unknown. Cystic fibrosis is characterised by disturbances in mucus secretion and electrolyte transport in epithelial cells. Our studies showing defective β-adrenergic regulation of secretion of mucus and amylase in cystic fibrosis submucosal tissues suggested alteration in a regulator protein beyond the site of cyclic AMP formation.

While investigating this hypothesis, data suggested alteration in biological activity of the regulator protein calmodulin, which mediates the actions of Ca²⁺ in cells. This was not due to altered amount of structure of calmodulin itself.

This change in activity of calmodulin was shown to correlate with alteration in a specific 61 000 molecular weight calmodulin-binding protein which showed a 21.6±6.0 (n=8 glands) fold increase in intensity of 125I-calmodulin binding in boiled cystic fibrosis extracts compared with control (n=3 glands).

Such an alteration in a protein which modulates the actions of calmodulin could explain (a) defective protein secretion and electrolyte transport in response to β-adrenergic stimulation and (b) widespread disturbances in Ca²⁺ homoeostasis seen in cystic fibrosis and thus might be related to the genetic defect.

**Placental potassium transfer.** T Mohammed, C Sibley, J Stulc, and M Maresh (Manchester).

Fetal potassium accretion rates are high and in the rat, the placenta may protect the fetus from maternal hypokalaemia. In humans fetal plasma potassium concentrations are reported to be higher than maternal at term.²

Potassium transfer was measured directly in the near term rat using placental perfusion. Following injection of radioactive potassium (K) or rubidium (Rb) Maternofetal clearance clₘᵣ or clₐₕᵢₐₙ="V/Q)/ A was measured after allowing time for a steady state to be achieved (V=venous perfusate and A=maternal plasma radioactivity. Q=flow rate). Fetoplacental (taken as a measure of fetomaternatal) clearance clₚ was measured for potassium from the steady state extraction of isotope added to the perfusate. clₘᵣ was significantly higher than clₐₕᵢₐₙ (158±13 v 82±8 μl min⁻¹ gram placenta⁻¹, p<0.01). These values are both 10 to 20 times higher than would be expected for diffusional-transport via a paracellular ‘pore’ pathway.³ clₚ was 124±13 μl min⁻¹ g placenta⁻¹ and calculated net materno fetal flux was 0.11 μmol min⁻¹ g placenta⁻¹.

Human cord ([K⁺]ₗ) and maternal ([K⁺]ₘ) plasma potassium concentrations were measured at elective caesarean section taking particular care to avoid hypoxia and haemolysis. Samples were taken from the cord immediately after the baby was delivered with placenta in situ and on three timed subsequent occasions after delivery of the placenta. [K⁺]ₗ at 5, 10, 20, and 30 minutes after laparotomy was 4-75±15, 5-95±26, 6-81±23 and 7-59±81 mmol. kg. plasma water⁻¹. [Km] was unchanged following laparotomy (4-30±13 & 4-26±23).

We conclude that there is active transport of potassium across the rat placenta. In the human the previously reported steady state maternofetal concentration difference at term is unlikely to be present. It is not yet clear whether [K⁺]ₗ and [K⁺]ₘ are similar because they are closely controlled or because human placental potassium transfer is mainly passive.


**Acute retinopathy of prematurity: risk factors.** YK Ng, AR Fielder, DE Shaw, and MI Levene (Leicester).

In a prospective study of retinopathy of prematurity (ROP) in infants of ≤1700 g birth weight, neonatal and ophthalmic data were obtained on 437 infants
(including 19 heavier twin siblings). 220 infants (50-3%) developed acute ROP and the maximum severity was stage 1 in 130 infants, stage 2 in 63, and stage 3 or 4 in 24 (one had stage 4). Notable significant variables (p=<0-0001) relating to stage 3 and 4 ROP were: lower birth weight and gestational age, longer duration of assisted ventilation and time spent in increased oxygen, more apnoeas and bradycardias which required action including those for which oxygen was necessary, respiratory distress syndrome, a persistent ductus arteriosus requiring treatment, positive blood cultures, longer duration of phototherapy, anaemia, and cranial ultrasound findings of haemorrhage. The occurrence of pneumothorax, and cranial ultrasound appearance consistent with periventricular leukomalacia were also significantly related to acute ROP (p<0-01).

In the infants in whom blood gases were monitored, only an arterial oxygen tension (PaO2) >15 kPa in the first two weeks was marginally significantly related (p=0-03) to the stage of ROP which developed. There was a highly significant relation (p=0.007) between PCO2 >13 kPa and acute ROP, and similarly with pH<7-2 (p=0-002) and base deficit of -8 or more (p=0-0004).

These results support the suggestion that the pathogenesis of ROP is multifactorial.

Heart and heart-lung transplantation in children: experimental or therapeutic? R Radley-Smith and M Yacoub (Harefield).

Since August 1984, 58 children under 15 years have undergone transplantation. Twenty seven patients aged 9 days to 14 years (mean 8-6) underwent heart transplantation. The main indications were dilated cardiomyopathy in 15 and congenital heart disease (CHD) in five. Thirty one patients aged 10 weeks to 14 years (mean 8-4) underwent heart-lung transplantation (HLT) for pulmonary vascular disease—primary in five and secondary to CHD in 16. Four patients had parenchymal lung disease. There were seven (26%) and 10 (32%) early deaths: moderate pulmonary hypertension in the recipient and bleeding from previous thoracotomy were significant risk factors in each group respectively. With a mean follow up of 20-2 and 13-6 months, there were one and two late deaths in each group. Postoperatively patients were maintained on cyclosporin and azathioprine. Routine steroids were not given. All patients are well, growing normally and attending ordinary schools. One patient developed lymphoproliferative disease which has regressed completely. Two patients after HLT developed obliterative bronchiolitis at 12 and 24 months, one patient required retransplantation. Routine annual reinvestigation has shown no evidence of chronic rejection in either group.

It is concluded that transplantation offers a chance of dramatic improvement in children with end-stage heart and lung disease, but long term function, particularly of the lungs, continues to need evaluation.

Infusion of T₃ restores the capacity of the pulmonary epithelium to reabsorb lung liquid in the hypothyroid fetal sheep. PM Barker, CA Ramsden, DV Walters, and LB Strang (London).

Lung liquid secreted by the fetal pulmonary epithelium needs to be reabsorbed from the alveolar space around the time of birth in preparation for air breathing. The capacity of the pulmonary epithelium to reabsorb this liquid depends on maturation of a sodium transport system which becomes increasingly sensitive to adrenaline towards the end of gestation.

Hypothyroidism resulting from thyroidectomy at 113–120 days’ gestation (term=147 days) in 12 fetal sheep significantly impaired maturation of the reabsorptive response to intravenous infusion of adrenaline (0·5 µg/minute). When dibutyryl cAMP was added to lung liquid, effectively bypassing the β receptor, the reabsorption characteristics were not restored, suggesting that hypothyroidism has its effect elsewhere in the sodium transport system. The reabsorptive response to adrenaline was seen to develop normally in two fetuses thyroidectomised at 118 days in which a constant infusion of triiodothyronine (T₃) (120 µg/day) was given from 125 (fetus A) and 126 (fetus B) days gestation.

Mean (SEM) lung liquid secretion (+) or reabsorption (−) rates before and during adrenaline infusion in control and thyroidectomised (T₃) fetuses of 135 days’ gestation and over

<table>
<thead>
<tr>
<th>n</th>
<th>Mean gestational age (days)</th>
<th>Before adrenaline (ml/hour)</th>
<th>After adrenaline (ml/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15</td>
<td>137.7</td>
<td>+15.2 (1.5)</td>
</tr>
<tr>
<td>T₃</td>
<td>13</td>
<td>139.7</td>
<td>+12.4 (1.3)</td>
</tr>
</tbody>
</table>

In T₃ infused fetuses the results were:
Fetus A (T₃+10 days T₃ infusion) | +21.4 | −4.0
Fetus B (T₃+10 days T₃ infusion) | +22.1 | −9.0

The triple X girl. SG Ratcliffe and G Butler (Edinburgh).

Sixteen girls with the triple X chromosome abnormality were identified at birth by cytogenetic screen-
ing of 34,380 consecutive liveborn infants and are participating in a longitudinal study together with controls from the same population.

The triple X girls had smaller head circumferences at birth and throughout childhood, presumably a reflection of slower brain growth. Febrile convulsions occurred in 37% of slower brain controls from 37% compared with 5% of controls. There was a significant lowering of IQ scores (verbal 88, performance 95, full scale 91), speech therapy was required by 50% and educational intervention by 80% (compared with 12% of controls). Behaviour in school, assessed by the Bristol Social Adjustment Guide, showed appreciable under-reaction.

Sexual development was delayed in onset by approximately 1½ years and one girl developed secondary amenorrhoea associated with a unilateral streak ovary.

The incidence of 1 in 1000 in the female population indicates that there will be around 25,000 triple X females in the United Kingdom yet the diagnosis is rarely made by paediatricians. Reports in the literature describe 16% of the offspring of triple X women to be chromosomally abnormal but this is likely to include biased reporting, and requires confirmation by continued study of population ascertained cases.

**Consequences of HIV infection in pregnancy: results from the European Collaborative Study.** Y Senturia (on behalf of the European Collaborative Study).

Since the end of 1985, there have been 351 HIV positive laboratory reports to CDSC on adult women in England and Wales; 57% reported between January and September 1987. This increase is likely to be paralleled by an increase in paediatric infection. Although the outlook for children with AIDS is poor, little is known about the outcome for the much larger proportion of HIV infected children who have less severe or asymptomatic infection.

European centres are collaborating in a prospective study to determine the prevalence of HIV infection in infants born to positive mothers, to examine risk factors for vertical transmission (such as maternal clinical status, breast feeding and mode of delivery), to establish the natural history of HIV infection in childhood and to identify precursors of AIDS/ARC onset in infected infants.

One hundred and fifty six children from six centres had been enrolled by 8 December 1987. Mothers of all children were known to be HIV positive at or before birth; 10% had ARC/AIDS prior to delivery. Ninety seven of the 156 children had been followed for at least six months and 70 for over one year. Eight had developed ARC/AIDS, five other children had substantial signs or symptoms, and 143 were clinically normal when last seen. Seventeen are known to be infected as assessed by virus culture, antigen test or persistence of antibody in the past 15 months: this is 20% of those whose infection status is known. The situation in March 1988, when 83 children will have reached the age of 15 months will be presented.

**Should paediatricians be more involved in the care of children with the most common cause of death and acquired handicap?** PM Sharples, A Storey, A Aynsley-Green, and JA Eyre.

Head injury is the most common cause of death and acquired handicap in children yet there has not been a detailed analysis of the management and outcome of such children by place or by person. We have performed a region wide study of all children admitted with or who died from a head injury between 1979–1986.

Children admitted with head injury to 53 hospitals in the Northern Region were identified from the Hospital Activity Analysis; the data concerning deaths were obtained from the death certificates supplied by the Office of Population Censuses and Surveys, the coroners’ reports and the hospital records.

Altogether 25,009 such children were admitted to hospital for a total of 49,195 bed days, thus, one child in every 200 is admitted with a head injury each year. There was an equal distribution of children across all ages. Forty eight per cent were admitted without being under the direct care of a neurosurgeon or paediatrician. Six hundred and three (2.4%) were transferred from a district general hospital to the Regional Neurosurgical Centres (RNSC).

Two hundred and fifty four (1%) died, 63% of whom were boys; 160 (63%) were >8 years old. Thirty three (13%) died at the roadside and a further 106 (42%) were dead on arrival to hospital; 116 (45%) died after admission, 83 (72%) at a RNSC and 33 (28%) at a district general hospital. Only 20% of those who died at the RNSC were under paediatric care and 74% under neurosurgeons and anaesthetists. Seventeen per cent of those who died at a district general hospital were admitted under paediatricians, the remainder were admitted under adult general or orthopaedic surgeons. The majority of those who died at a district general hospital survived more than six hours and could have been transferred to a specialist unit. At least 25% of all children who died had potentially preventable causes of death.
Disquieting facts are revealed by these data. Further detailed analysis of the management of these children is being performed to define the services and the facilities that should be provided for optimal care both at the roadside and in hospitals.

We thank Action Research and Newcastle Health Authority.

Jejunal epithelial transport in cystic fibrosis. CJ Taylor, J Hardcastle, P Hardcastle, and P Baxter (Sheffield). Cystic fibrosis is characterised by a defect in chloride transport in sweat duct and respiratory epithelial cells. We have recently demonstrated a similar defect in electrically monitored chloride secretion in gut epithelium, using a modified Ussing chamber technique. Jejunal biopsy samples from children with cystic fibrosis failed to respond when challenged with the intestinal secretagogues acetylcholine (ACH) and prostaglandin E\(\text{2}(\text{PGE}\text{2})\), while control tissue exhibited a rise in potential difference (pd) and short circuit current (SCC) in response to these agents.

Further studies have been performed on biopsies from six children with cystic fibrosis (mean age 6-8 years) and six controls (mean age 4-9 years) using both 5 hydroxytryptamine (5HT) and agents acting intracellularly (dibutyryl cyclic AMP [dB cAMP] and the calcium ionophore A23187). Control tissue responded to all these secretagogues with an increase in pd and SCC. No response was obtained in cystic fibrosis biopsies to either the receptor mediated agents or dB cAMP although an increase in pd and SCC was observed with mucosal sodium linked glucose absorption. Four cystic fibrosis tissues also responded to A23187 with an increase in SCC. Failure to respond to this wider range of secretagogues suggests that the defect in cystic fibrosis is at a common intracellular point that mediates secretion, beyond the generation of cAMP. The response to A23187 would indicate that there is a failure to elevate or release ionised intracellular calcium.

Campylobacter pylori gastritis can be diagnosed serologically? JE Thomas, EJ Eastham, TSJ Elliott, DB Berkely, and D Jones (Newcastle upon Tyne and Manchester). The aim of this study was to investigate the usefulness of anti Campylobacter pylori (Cp) antibody titres in relation to endoscopically proven active chronic gastritis in children aged 5–16 years. Antral biopsies were obtained from 51 consecutively endoscoped patients and examined by culture, histology and scanning electron microscopy. Specific IgG antibodies to Cp were measured using a sensitive ELISA assay. Aged matched controls were obtained from a hospital based population with no significant gastrointestinal symptoms.

The endoscopic results confirm the presence of Cp in 21% of patients and a strong association with active chronic gastritis. All patients with Cp had circulating specific IgG antibodies, with positive titres of >1:1600. Their presence was 100% sensitive and specific. In the control group only two of 51 patients (3-9%) had positive titres, in each case not exceeding 1:1,600. We conclude that Cp associated gastritis is associated with high circulating levels of specific IgG antibody and that their measurement is a useful investigation in children with upper gastrointestinal symptomatology.

Systemic Haemophilus influenzae type b disease in children in the Oxford region: implications of current conjugate vaccine trials. G Tudor-Williams, J Frankland, D Isaacs, RT Mayon-White, JA Macfarlane, MPE Slack, E Anderson, P Crook, and ER Moxon (Oxford). Since January 1985 a prospective study of invasive Haemophilus influenzae type b (Hib) disease in children in the Oxford region has been in progress. One hundred and fifty one cases of the type b (Hib) infection have been identified in the first 2½ years of the study. Ninety six per cent occurred in children <5 years, 70% <2 years and 10% <6 months. Meningitis accounted for 67%, epiglottitis 11%, cellulitis 8%, pneumonia, joint infections or bacteraemia amounted to 14%. In an estimated population 169 300 children aged <5 years, the cumulative risks of invasive infection and meningitis respectively are 1:645 and 1:950 children. There were four early deaths, all in children aged over 6 months.

Hib capsular polysaccharide (PRP) has been shown to be poorly immunogenic under 2 years of age. Conjugation of PRP with protein enhances its immunogenicity in infancy. Several candidate vaccines have been produced, and the first efficacy trial of one such conjugate (PRP-D) in Finland has demonstrated an 87% protective efficacy (95% confidence interval=50–96%) in children immunised under 6 months. We are conducting a safety and immunogenicity study of a more highly characterised conjugate (capsular oligosaccharide covalently linked to a mutant diphtheria toxin, the HB-O-C vaccine), two doses of which have been shown to stimulate significantly higher concentrations of antibody than three doses of PRP-D. Ninety five per cent of this region’s children
receive at least two doses of DPT and polio; assuming a 90% efficacy for the HbO-C vaccine, incorporation of this into the primary immunisation schedule has the potential for preventing 42 cases of invasive Hib disease annually in the Oxford region.

The outcome for infants of less than 28 weeks' gestation. AM Weindling and RWI Cooke (Liverpool).

Offering intensive care to infants of <28 weeks is often questioned because of the possibility that the proportion of handicapped children may be increasing.

We have examined the outcome of 477 infants of 28 weeks and less born between 1980–1985 from Merseyside and North Wales and nursed at this hospital. Two hundred and fifty five survived. Seven were lost to regular follow up. All the others were assessed annually by general physical and neurological examinations with developmental screening. Impairment was defined as moderate to severe developmental delay, cerebral palsy of any degree, or hearing or visual impairment sufficient to compromise developmental progress.

Three hundred and seven infants were born at <28 weeks' gestation and 126 (41%) survived. This compared with 170 infants born at 28 weeks with 122 (72%) survivors. Survival over this six year period improved slightly from 38% to 44% for infants <28 weeks and from 60% to 70% for infants of 28 weeks.

There was a gradual and steady decline in the proportion of disabled survivors. In 1980, 38% of surviving infants <28 weeks and 27% of 28 weeks survivors were disabled. In 1985 the comparable proportions were 20% (<28 weeks) and 11% (28 weeks). The number of disabled infants expressed as a percentage of total births also declined from 15% in 1980 to 8% in 1985.

No infants of 23 weeks' gestation or less survived, although 3/31 infants of 24 weeks survived, all without disabilities.

The predictive value of somatosensory evoked potentials in the preterm infant. CP White, VJ Klimach, and RWI Cooke (Liverpool).

Somatosensory evoked potentials (SEPs) provide information about the functional integrity of the sensory system. The anatomical proximity of the motor and sensory pathways means that damage to the sensory pathways, as reflected in abnormalities of the SEP, may also imply damage to the motor pathways. Thus SEPs may prove useful in the prediction of neurological handicap in this group of high-risk infants.

Thirty infants with ultrasound abnormalities were tested in the neonatal period and their results compared with those of 'normal' infants of corresponding gestational age. Many had abnormally long latencies or absent responses. At 2 years of age these children have been assessed for the presence of cerebral palsy or developmental delay.

Seventy seven per cent of those infants with abnormal SEPs have signs of cerebral palsy and a further two children have delayed development. Eighty three per cent of infants with normal SEPs have no neurological abnormalities, however two children with normal SEPs have developed spastic diplegias.

Thus SEPs provide another method of predicting neurological outcome in the preterm neonate.

The temporal pattern and natural history of asthma in childhood. S Zeidan, H Ali, MJ Danskin, and EN Hey (Newcastle upon Tyne).

All 2700 of the 7 year old children in North Tyneside were screened for wheeze in 1979 with a questionnaire followed by selective clinical assessment (including bronchial challenge): 98% of the families responded to the questionnaire and 9-3% of the surveyed children had had episodic wheeze in the previous 12 months. The symptoms of all those who were followed responded to one or more of the drugs used in the management of asthma, but only 12% of the symptomatic children were known by the parents to be asthmatic prior to the survey, and only 27% had previously had consistent bronchodilator treatment.

When the same cohort of children were reassessed eight years later (92% of survey forms returned), a third of those had had symptoms at 7 were now asymptomatic, but 100 new cases of asthma were found amongst children who had had no recognisable symptoms (according to parental questionnaire) in 1979. The point prevalence of asthma in children at 15 was, therefore, only marginally less (8-6%) than it had been at 7.

More seriously, only 58% of the children who first developed recognisable symptoms after 1979 had yet received symptomatic bronchodilator treatment by the time the second survey was conducted, and only 53% knew that their symptoms were due to asthma. The School Health Service needs to recognise that many children who are asymptomatic at 7 develop troublesome asthma in later childhood. Previous longitudinal, community based, surveys have failed to highlight this issue.

Asthma still remains underdiagnosed and undertreated.

During the period September 1985–August 1987, 653 consultant paediatricians in the United Kingdom and Eire cooperated in a prospective study by completing monthly questionnaire cards, and by providing subsequent clinical information. Additional information was collected from the microbiologists, the CDSC, and OPCS. Altogether 1973 cases of meningitis were reported; M/F ratio 1:3/1. Four hundred and nine occurred during the neonatal period of whom 289 were bacteriologically proven—1/4000 live births. Group B streptococci (GBS) (25%) and E coli (17%) were the commonest isolates. H influenzae, Str pneumoniae and N meningitidis accounted for 13% of cases and L monocytogenes for 5%. In 5% of neonates treatment was based on chloramphenicol, in 24% on gentamicin and in 14% on cefotaxime. The overall mortality among the newborn was 20% (ranging from 30% with enteric G -ve rods to 0% when listeria or viruses were isolated). Culture negative cases of meningitis had a 3% mortality. Among babies older than 28 days Str pneumoniae (12%), H influenzae (36%) and N meningitidis (34%) accounted for 82% of cases and E coli or GBS for 6%. Mortality among babies over one month of age was 5%. The incidence was lowest in the Yorkshire and SW Thames Regions and highest in Northern Ireland and the SE Thames Regions. This is the largest and most comprehensive study of neonatal and infantile meningitis in the British Isles and in due course it will allow data on long term morbidity to be collected.


Enlarged tonsils and adenoids are the major cause of upper airway obstruction in children. However, the prevalence of such obstruction has never been determined. The main aim of this study was to establish how many children with adenotonsillar hypertrophy suffer night-time hypoxaemia. We also wished to identify the clinical features of those who do.

So far, 42 patients have been studied preoperatively. Oxygen saturation (SaO2), chest movement and ECG were recorded overnight. Awake SaO2, mean SaO2 during sleep and dips in SaO2 >10% below baseline were noted. Nineteen controls have also been studied.

All controls had mean SaO2 values above 92-0% and less than one obstructive episode per hour. Eleven patients had mean SaO2 ≤92-0% and 10 had obstructive episodes. In nine patients restudied postoperatively all these abnormalities were abolished.

A close association was found between awake and mean asleep SaO2; seven of 11 patients with awake SaO2 ≤95%, but only four of 30 with awake SaO2 >95% had a mean SaO2 ≤92-0% (p<0.01). Preliminary analysis in 27 patients shows that those who obstruct have significantly more airway, but not infective, symptoms than the remainder.

Thus children with adenotonsillar hypertrophy and night-time obstruction are common and can be identified in outpatients by their symptoms and SaO2 whilst awake.

We thank the MRC for support.

Detection of pulmonary surfactant in amniotic fluid by polarised light microscopy. HW Clark, W Jacobson (Cambridge).

Jacobson et al (1988) have reported the detection of pulmonary surfactant in tracheal aspirates by polarised light microscopy. Could this technique be used to detect the presence of surfactant in samples of amniotic fluid at birth to assess the risk of development of respiratory distress syndrome?

Altogether 136 samples were examined. Of 61 samples from births, 11 were of 24–35 weeks' gestational age and 50 were of >36 weeks. Seventy five samples were collected by amniocentesis at 16 weeks.

The unprocessed fluid was examined microscopically in polarised light for evidence of birefringent particles. The 50 specimens from mature fetuses contained one main type of particle which was identical to that observed in tracheal aspirates: these were round (0.5–3 μm diameter), strongly birefringent, and showed a cross of polarisation indicating layers of phospholipid. They were soluble in a 2:1 (v/v) mixture of chloroform:methanol.

Of the 11 premature samples, seven showed these particles, but four showed either none or very few and these four infants developed respiratory distress syndrome. None of these characteristic particles was observed in the 75 samples from amniocenteses.

Some particles of vernix are large (8–12 μm diameter) with a cross of polarisation and easily distinguished from the particles of surfactant. There was a good correlation between the presence of surfactant particles and the percentage of phosphatidyl choline in the sample.

Polarised light microscopy may thus provide a simple test for surfactant in amniotic fluid which could be useful in the diagnosis of respiratory distress syndrome.