B P A S U

British Paediatric Association Surveillance Unit

Supported by the Medical Research Fund of Children Nationwide

BRITISH PAEDIATRIC ASSOCIATION SURVEILLANCE UNIT (BPASU)

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The BPASU positively encourages recipients to copy and circulate this report to colleagues, junior staff, and medical students. Additional copies are available from the BPASU office, to which any enquiries should be addressed.

1 Acknowledgements

As in previous years the BPASU thanks the Children Nationwide Medical Research Fund for its continued financial support. We thank the Muirhead Trust for supporting the development costs of new computer equipment and Allen and Hanburys for supplying the protocol booklets.

In 1995, the surveillance unit held its first scientific seminar; we extend our thanks to the Sir Jules Thorne Trust, Serono, Roche, and Pasteur Mérieux MSD for their support.

Thanks are due to the British Paediatric Association for its continued support. Finally, we also thank members of the British Paediatric Association, the Faculty of Paediatrics of the Royal College of Physicians of Ireland, and the many other clinicians and pathologists who have contributed reports and data to the BPASU, and through it to the researchers who use the unit. Without these contributions the BPASU would not be the world leader that it is.

BPASU Executive Committee
December 1995

2 Chairman's review

Since its inception in 1986 the surveillance unit has undertaken 39 studies. These have led to original scientific findings, generated many presentations and publications, informed policy decisions, and educated or informed those taking part in surveillance.

A number of important findings have been made through surveillance this year. The study of **HIV and AIDS in childhood** shows how a study can answer important questions, and how data gathered from paediatricians become more powerful when combined with data from other sources. Obstetricians, microbiologists, and unlinked anonymous surveys also contribute to surveillance and when their data are combined with those from paediatricians it can be seen that only a small proportion of pregnancies in HIV infected women are detected before childbirth. This finding led directly to further emphasis being given by the Department of Health to its policy of making antenatal testing routine in London and of encouraging testing of women at higher behavioural risk elsewhere.

Reye's syndrome has been monitored by the unit and its British Paediatric Association (BPA)/Public Health Laboratory Service (PHLS) predecessor since 1981. Early on, data helped demonstrate a causal link with the use of aspirin in children. Experience since then, in the United Kingdom (UK) and elsewhere, has given no reason to doubt the recommendation that aspirin should not be given to children. This recommendation is not followed throughout Europe where surveillance for Reye's syndrome is now improving in some areas, mostly through the development of surveillance and surveillance units copying the British model (see below). It will be important therefore to continue monitoring Reye's syndrome in the UK and Éire so that a reliable baseline incidence can be monitored in a country where aspirin is rarely used. I hope that this survey will be supported and remain on the BPASU card. Some cases of Reye's syndrome reflect an underlying metabolic disorder, one of which is **medium chain acyl-CoA dehydrogenase deficiency** and this condition is also under surveillance.

The survey of **neonatal necrotising enterocolitis** was the first national study of this condition in any country. It placed a heavy burden on paediatricians responsible for neonatal units, but its cohort of nearly 300 confirmed cases represents an important national resource for the study of factors that cause the condition and the best methods of management.

Reports of **congenital rubella** rose slightly in 1994. Following the general success of the measles and rubella (MR) campaign in the autumn of 1994 in improving immunity against rubella among children, it has been decided to stop the selective immunisation policy. The major problem will remain, as it is now, with recent immigrants. It will be important to maintain surveillance of congenital rubella to audit the effectiveness of control measures. I am grateful that this surveillance is being maintained following a generous grant from the PHLS. It is also hoped that the MR campaign has reduced the incidence of measles to minimal levels, but it is proving impossible to interrupt transmission fully. As there will always be imported cases I am glad to see that **subacute sclerosing panencephalitis (SSPE)** has returned to the orange card. Both of these conditions are examples in which surveillance is improved by combining reports from laboratories and other specialities. This year one case of SSPE was detected through close reading of the *Big Issue*!

The survey of **haemophagocytic lymphohistiocytosis** ended in 1994. This study has helped to establish a clinical network for basic research. Studies are underway using patients identified to attempt to see if there is an underlying genetic susceptibility at least in some groups of children with this rare but important condition.

The survey of **congenital syphilis** and a related survey of syphilis treated in pregnancy carried out by specialists in genitourinary medicine and laboratory reporting are providing a resource that will allow antenatal syphilis screening in the UK to be evaluated.

I am pleased that the surveillance unit tackles areas of social paediatrics such as the survey of **alleged Munchausen syndrome by proxy/non-accidental poisoning and suffocation**. This survey has been difficult to carry out and its researchers are to be congratulated on its completion in August 1994. We now look forward now to its findings. Because of the sensitivity of this topic the researchers have chosen not to publish results in this year's annual report.

The survey of **invasive *Haemophilus influenzae* infection** previously confined itself to apparent vaccine failures – that is, where invasive infection had seemingly taken place despite prior vaccination. Since the successful introduction of *H. influenzae* type B (Hib) vaccination in 1992, the number of invasive Hib cases in children has fallen to such an extent that it is possible to expand this surveillance to incorporate all invasive Hib, including the routine surveillance data received by the PHLS. As the UK remains unique in Europe in not having a Hib booster, it still will be important to maintain surveillance for apparent vaccine failure.

One of the BPASU's major strengths is its ability to respond rapidly to public health emergencies. This is

shown by the study of **vitamin K deficiency bleeding**, which was relaunched in 1993 in response to a trend towards the use of oral vitamin K in newborn babies. The full results of this survey are being analysed but the preliminary results do not show a major upsurge of deficiency bleeding following the switch to oral administration. A similar rapid response was shown for the survey of **adverse neonatal outcomes of delivery or labour in water**. Many surveillance unit studies are combined with studies elsewhere or form parts of programmes. In this case a survey of the extent of delivery/labour in water was undertaken by the National Perinatal Epidemiology Unit in Oxford.

In the past year debate has continued about the advisability of postnatal screening for jaundice. The survey of **biliary atresia** will contribute information needed to make rational decisions about screening.

The surveillance unit has maintained a number of studies on diabetes. In 1994 the unit began surveys of **transient or permanent neonatal diabetes** and **cerebral oedema following diabetic ketoacidosis**, the commonest cause of mortality from diabetes in childhood. Another new survey in 1995 was **pyridoxine deficiency**, a rare but important cause of epilepsy.

The high point of 1994 for the surveillance unit was its **first scientific seminar**. This event was unusual in that rather than presenting results of individual surveys it critically reviewed the progress and value of the unit. Presentations concentrated on successes and failures, difficulties in combining data from different sources, ethical, and international aspects of surveillance. It was stimulating to find an audience from many countries that represented public health, the Department of Health, research and advocacy bodies, as well as BPA members. Part of the rationale was to provide a crash course for those considering studies. It is gratifying to note that a small flock of studies have been proposed since the workshop. I am grateful to all those who prepared presentations, to Dr Diana Walford and the PHLS for their hospitality, and to the commercial supporters who allowed the event to 'break even' with only a modest registration fee. I am pleased to report that the unit's executive committee has set up a small group to plan the next seminar for 1996.

The BPASU's success and value is recognised internationally. Almost identical surveillance units have been established among British neurologists and occupational health physicians. Overseas, surveillance units based on the BPASU model are now well established in Australia, the Netherlands, and Germany. Surveillance units have also started recently in Switzerland and Malaysia, and close links are developing between the national units. In February Professor Pauline Verloove van Horick organised a representative meeting from the European units in Leiden, from which a series of international papers were submitted to the Conference of the European Society for Paediatric Research. Three of the units attended the scientific seminar in June.

As recorded in my last review the unit's name was changed in mid-1994 from the British Paediatric Surveillance Unit (BPSU) to the British Paediatric Association Surveillance Unit (BPASU) while retaining its autonomy within the larger BPA and its Research Unit. Throughout this report BPASU is used for uniformity, although many studies began before the unit's name was changed. The change of name recognised the prime contribution of BPA members to the unit but was not intended to downgrade the contribution from other sources of data and professional colleagues to its public health and scientific value. This was emphasised at the BPA's 1995 annual meeting when its president emphasised to paediatricians the importance of reporting to the unit. I am particularly grateful to Roy Meadow for the personal support he has given the unit during his term of office.

1995 has seen some administrative changes. Ruth Gilbert had to resign as one of the medical advisors to lead a new centre for evidence based child health. As a number of BPA members know, her contribution in helping to guide and improve studies was considerable. To replace Ruth the Executive Committee took the novel approach of advertising. Although the post is unpaid and the work 'unsung' more than one application was received. I am delighted to welcome Margaret Guy, from a background of public health and paediatrics, who is joining Angus Nicoll, the other medical advisor. I would like to particularly thank Angus for his important contribution in the past year. Richard Lynn the scientific coordinator and Myra Schetman his assistant are the core of the unit. Richard has been immensely productive this year and much of the success of the seminar must be due to his organisational skills. I am also grateful to Jon Pollock for the energy he has put into fund raising.

Financial responsibility for the BPASU now lies with the BPA through its Research Unit. As a professional membership organisation the BPA requires the Research Unit to fund its own work, including that of the BPASU. Obtaining external sources of funding to manage investigations of rare and sometimes little known conditions is a challenge. The BPASU Executive Committee takes the view that long term sponsorship of the unit's work is highly desirable, to ensure continuity for a programme that relies heavily on the reporting system being a natural and regular long term component of a paediatricians' clinical work. The Executive Committee deserves special mention for the many afternoons it puts in during the year. Finally I would like to thank members of the BPA. The unit boasts a 94% reporting rate by BPA members, a percentage which is at least the equal of any reporting system worldwide.

Professor Catherine Peckham
Chairman BPASU Executive Committee

3 Introduction

The British Paediatric Association Surveillance Unit (BPASU) began its work in June 1986, and represents paediatricians in the United Kingdom and the Republic of Ireland. The BPASU enables paediatricians to participate in the surveillance of infections and infection related conditions and promotes the study of uncommon disorders. It provides a mechanism by which new diseases can be detected, monitored, and investigated swiftly.

Several agencies collaborate in the BPASU: the British Paediatric Association (BPA), the Public Health Laboratory Service (PHLS), the PHLS Communicable Disease Surveillance Centre (CDSC), the Department of Epidemiology at the Institute of Child Health, University of London (ICH), the Scottish Centre for Infection and Environmental Health in Glasgow (SCIEH), which administers the scheme in Scotland, and the Faculty of Paediatrics of the Royal College of Physicians (Ireland). The BPASU monitors conditions of importance to public health, and observers from the Department of Health and the Office of Population Censuses and Surveys (OPCS) attend BPASU committee meetings.

The reporting system

Participants of the reporting system include consultant paediatricians who are members of the BPA, the Faculty of Paediatrics of the Royal College of Physicians of Ireland, and since 1992, selected members of other specialties. The BPASU has extended its activities through a study on congenital dislocation of the hip undertaken with the British Orthopaedic Association (BOA) and is currently liaising with the Royal College of Ophthalmologists.

Participants are sent a card and a set of instructions each month, on which the disorders under surveillance are listed. Respondents are asked to return the card to the BPASU office each month, reporting the number of cases of each disorder seen in the preceding month. Compliance with the scheme is constantly monitored: participants are expected to return cards even if no cases are reported.

Case reports are followed up. The BPASU office informs the relevant research team, who contact the reporting paediatrician for further information, in accordance with a study protocol for the condition reported. The research team then reports back to the BPASU on the outcome of follow up, confirming cases, identifying duplicates, and reporting errors. The research team is employed by the institution that undertakes the research.

A distinctive and powerful feature of the BPASU system is the use of complementary sources of information alongside data from paediatricians. This allows sources to be validated and gives a more complete picture of a disease or condition. The first complementary source to be used was laboratory reports of infections from the PHLS. Other sources, such as death entries (OPCS) and completed consultant episode data are also used. The use of multiple sources improves ascertainment of cases. Completeness of ascertainment varies considerably between studies and conditions, according to the ease of ascertainment and the availability of complementary sources.

This report covers the calendar year 1994, but also refers to studies and activities that have begun in 1995.

4 How the BPASU works

Selection of studies

A study is eligible for participation in the scheme if its subject is a rare childhood disorder (or rare complication of a commoner disease) of such low incidence or prevalence as to require cases to be ascertained nationally in order to generate sufficient numbers for the study. Particular priority is given to studies of importance to public health but all studies have to conform to high standards of scientific rigour and practicality. The system is open to any clinician or research group, but applicants are encouraged to approach the BPASU with or through a paediatrician or paediatric department.

The number of conditions under surveillance is usually limited to 12 and there is keen competition for places on the BPASU card. Occasionally, the capacity of the reporting card has been increased to accommodate 14 rather than 12 conditions. The unit receives an average of 30 general enquiries about potential studies each year; many are eventually incorporated into the reporting card. About 25 studies are currently in various stages of development.

The unit has recently adopted a two phase procedure to process applications quickly. In phase one, a short study protocol is submitted, covering no more than two sides of A4 paper. This should include background to the proposed study, a case definition, questions that the study aims to answer, and details of financial and academic support. At this stage the scientific coordinator and medical advisers can offer guidance on the application before it is submitted to the BPASU Executive Committee.

Many studies are found to be unsuitable at phase one for a number of reasons. The condition may be too common and therefore place too great a burden on paediatricians for reporting or follow up; there may be no suitable case definition; the aim of the study may constitute audit rather than surveillance and research; and data may be obtained easily elsewhere. In addition source studies present insuperable practical difficulties. Once the Executive Committee agrees that the protocol is suitable, the second phase of the application is requested. This should provide full details of the methodology and aims of the study. The applicant presents the details to the Executive Committee, which meets monthly and consists mainly of consultant paediatricians (general and specialist) and epidemiologists. Factors that determine whether an application is accepted include those listed in the box.

If necessary the BPASU will help potential investigators (especially those with less experience in research methods) in improving potentially valuable studies. If a study is not accepted, the Executive Committee always tries to advise the applicant on alternate means of collecting data.

Factors that favour acceptance by the BPASU

- rarity, but short term or geographically limited studies of commoner disorders are considered.
- proposals with outcomes of clear importance to public health.
- scientific importance.
- uniqueness, priority will not be given if similar studies have recently been undertaken or if other data sources are readily available (although BPASU encourages the use of alternative data sources for validation).
- quality, in terms of clear achievable objectives, practicability, patient confidentiality, and resources.
- workload placed on the reporting paediatricians.
- ethical approval if appropriate.

Mailing system

The BPASU works on the principle of 'active' reporting. The stimulus for a clinician to report is a card with a 'menu' of reportable disorders, sent each month by the BPASU office to consultant paediatricians. The office updates its mailing list with changes sent in by members, and by monitoring new consultant appointments. The card is accompanied by instructions for reporting and case definitions. When a new study begins, the mailing includes a study protocol with details about the study. Respondents tick a box by each of the conditions that have been seen in the preceding calendar month. If no patients with any of the disorders have been seen, there is a 'nothing to report' box to mark: this is an essential feature of the system because it monitors compliance and detects non-responders who may have moved or retired. Respondents who have not returned their card for three consecutive months are sent reminders. Scottish paediatricians return their completed cards to the BPASU office by way of the Scottish Centre for Infection and Environmental Health.

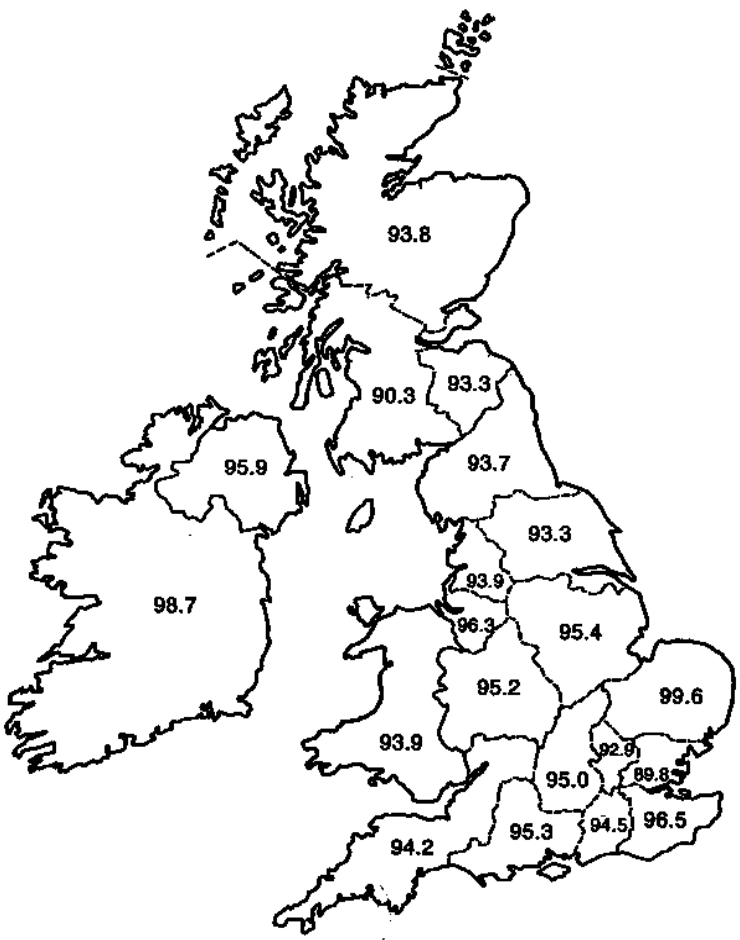
Participation

The number of paediatricians who participated in the scheme in 1994 rose from 1236 in January to 1364 in December, an increase of about 10% during the year. By June 1995 there were 1406 respondents. The overall response rate in 1994, calculated as the percentage of cards returned within 60 days of mailing, was 94.4% (14920/115810) a rise of 2.6% compared with 1993. The range of response rates extended from 91.9% (1254/1364) in December to 96.1% (1217/1266) in February, with a median of 94.3% in January and May.

Response rates varied considerably between regions (figure 1); East Anglia (99.6%) had the highest response rate, and North East Thames the lowest (89.6%).

The BPASU has developed databases for additional respondents to help ascertain cases of particular conditions that are seen by specialists other than paediatricians. For example, to help ascertain cases of haemophagocytic lymphohistiocytosis and biliary atresia the BPASU set up, in May 1992, an additional database of pathologists who were not members of the BPA. This group achieved a mean response of 80% in 1994. Although this response rate was lower than for BPA members, it still represents a good response for a clinical surveillance system.

Figure 1 Average response rate (%) by region, 1994



Overall average response rate = 94.4%

5 Cases reported to the BPASU (up to October 1995)

Cumulative reports

For the year ending December 1994, a total of 828 cases have been reported (table 1). Four hundred and forty-four of the 828 cases have been confirmed as positive reports by the researchers who feed this information back to the BPASU. This figure will alter as outstanding data are collected. It should be noted that the confirmed cases (to October 1995) in table 2 exclude reporting errors and duplicates. The numbers of cases in table 1 may differ slightly from those in the research articles that follow, for reasons of definition, including ascertainment from sources other than the BPASU.

Reports by respondents

BPASU continually monitors the workload of respondents in terms of reporting and completion of follow up questionnaires (figure 2). Nearly three quarters of respondents (71%) reported no cases in 1994; 27% reported between one and four cases, and only 1% reported five or more cases. The overall need to report cases fell in 1994 due in part to the completion of surveys on congenital dislocation of the hip and neonatal necrotising enterocolitis.

Table 1 *Cases reported: June 1986 to December 1994 (confirmed by October 1995)*

Condition under surveillance	Date when reporting began	Reports (confirmed cases)									
		June 1986 to Dec 1987		Jan 1988 to Dec 1989		Jan 1990 to Dec 1991		Jan 1992 to Dec 1993		1994	
AIDS/HIV	June 1986	60	(37)	77	(49)	378	(296)	228	(156)	107	(61)
Reye's syndrome	June 1986	80	(38)	69	(37)	52	(20)	40	(16)	13	(2)
Subacute sclerosing panencephalitis (SSPE)	June 1986	50	(32)	34	(18)	45	(26)	24	(10)	12	(6)
Congenital rubella	Jan 1991	–	–	–	–	32	(19)	19	(11)	13	(8)
Acute flaccid paralysis	July 1991	–	–	–	–	49	(34)	87	(68)	17	(10)
Haemophagocytic lymphohistiocytosis	Sept 1991	–	–	–	–	16	(10)	57	(28)	19	(12)
Haemophilus influenzae b vaccination failures	Sept 1992	–	–	–	–	–	–	78	(56)	29	(20)
Munchausen syndrome by proxy/Non-accidental poisoning, suffocation	Sept 1992	–	–	–	–	–	–	157	(98)	67	(37)
Vitamin K deficiency bleeding	Jan 1993	–	–	–	–	–	–	64	(20)	48	(11)
Biliary atresia	March 1993	–	–	–	–	–	–	7	(10)	89	(8)
Congenital syphilis	July 1993	–	–	–	–	–	–	6	(5)	4	(2)
Neonatal necrotising enterocolitis (NEC)	Sept 1993	–	–	–	–	–	–	107	(81)	322	(216)
Medium chain CoA acyl dehydrogenase	March 1994	–	–	–	–	–	–	–	–	49	(27)
Water births	April 1994	–	–	–	–	–	–	–	–	30	(23)
Transient and permanent neonatal diabetes	April 1994	–	–	–	–	–	–	–	–	9	(1)
Total		190	(107)	180	(109)	572	(405)	874	(559)	828	(444)

Excludes previously completed studies (see page 37).

AIDS/HIV – reports of AIDS in June 1986 included all cases previously seen; case definition extended to include HIV infection in January 1990.

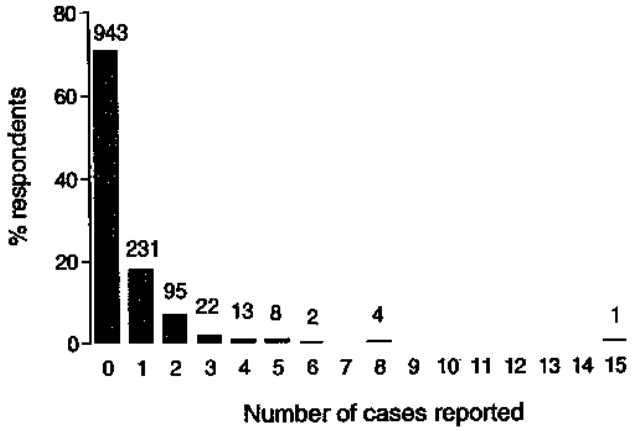
SSPE – reports of SSPE in June 1986 included all cases seen in the previous 12 months; reports 'not confirmed' include those outside England and Wales which are not followed up by CDSC. This survey ended in June 1994.

Acute flaccid paralysis – this survey ended in July 1994.

NEC – this survey ended in October 1994.

Water births – adverse effects of labour/birth in water.

Figure 2 Respondent workload (number of respondents shown above columns)



Follow up and confirmation of reports

When a clinician returns a report indicating that he/she has seen a case of one of the conditions being studied, BPASU sends the reports to the appropriate research team, who contact the reporting clinician and elicit further clinical details using a short questionnaire. The researchers then assess the details, informing BPASU whether or not the case met the study definition or whether the case had been reported already (this is particularly likely for diseases that require tertiary referral). The time taken to follow up a report varies greatly between conditions and may be longer if microbiological or pathological details are needed to confirm a case.

BPASU is encouraged by the rate at which reports are followed up. We considered the studies active up to the end of 1994, and found that only 295 of 2710 initial reports (11%) had yet to be followed up. Our experience has shown that this figure falls as studies near completion. The final proportion of reports that are successfully followed up averages between 95% and 100%. This very high compliance rate is vital for the success of the BPASU and the studies it coordinates.

Table 2 provides evidence for the accuracy of reporting. Four hundred and sixty-two case reports (17%) received for the active studies were later identified as reporting errors (misdiagnosis, case definition not met, or wrong box marked on the reporting card).

Outcome

Valid report: Case followed up and confirmed by research worker as both unique (that is, not a duplicate) and satisfying the diagnostic criteria. Valid reports include cases reported to the BPASU but already known to the research worker from another source.

Invalid report: Duplicate report from within the BPASU scheme. Reporting error – for example, ticked wrong box, diagnosis revised, uncertain case that does not meet definition, or unable to follow up.

Not yet known: Details not yet received by BPASU from research workers (as of October 1995).

Table 2 Outcome of the follow up for cases reported up to December 1994 (see box for definitions)

Condition under surveillance	Valid reports	(%)	Invalid reports: Duplicates	Errors	(Total %)	Not yet known	(%)	Total reports
AIDS/HIV	603	(71)	115	118	(27)	14	(2)	850
Reye's syndrome	114	(45)	35	96	(52)	9	(3)	254
Subacute sclerosing panencephalitis	92	(56)	23	29	(32)	21	(12)	165
Congenital rubella	38	(59)	13	13	(41)	0	(–)	64
Acute flaccid paralysis*	112	(73)	26	5	(20)	10	(7)	153
Haemophagocytic lymphohistiocytosis*	50	(54)	24	6	(33)	12	(13)	92
Haemophilus influenzae type B*	76	(71)	6	24	(28)	1	(1)	107
Non-accidental poisoning, suffocation/ Munchausen syndrome by proxy	131	(58)	43	46	(40)	4	(2)	224
Vitamin K deficiency bleeing	31	(28)	10	33	(38)	38	(34)	112
Biliary atresia	18	(11)	4	9	(8)	131	(81)	162
Congenital syphilis	7	(70)	0	1	(10)	2	(20)	10
Neonatal necrotising enterocolitis	297	(69)	46	65	(26)	21	(5)	429
Medium chain CoA dehyrogenase	27	(55)	12	8	(41)	2	(4)	49
Water births	23	(77)	5	2	(23)	0	(–)	30
Transient & permanent neonatal diabetes	1	(11)	1	7	(89)	0	(–)	9
Total	1620	(60)	363	462	(30)	265	(10)	2710

* Studies in which validation depends on microbiological/pathological details.

6 Funding

BPASU asks research teams to contribute a sum of money each month to the unit to cover the start up costs of a study, printing and distribution of cards, and administration costs for a study. In 1994–1995 the sum was £165 each month. After assessment of the future needs of the BPASU, the suggested contribution rate was set at £185 each month for 1995–1996. Contributions from researchers met 35% of the BPASU's running costs in the financial year 1993–1994. The remainder of the unit's costs were covered by a grant from the Children Nationwide Medical Research Fund.

7 Conditions included

This section summarises the background, objectives, and progress of the 15 studies undertaken during 1994. Three studies began in 1995 and these are described in section 8.

Table 3 *Studies underway in 1994*

Page	Study	Principal researchers	Research institutions
10	AIDS/HIV infection in childhood*	P Tookey, A Nicoll, D Goldberg	ICH (London), PHLS, SCIEH
11	Reye's syndrome*	M Catchpole, L Newton	PHLS
13	Neonatal necrotising enterocolitis	R Abbott, A Lucas	Dunn Nutrition Unit, Cambridge
14	Congenital rubella*	G Jones, P Tookey, C Peckham	ICH (London)
15	Subacute sclerosing panencephalitis	E Miller, N Begg	PHLS
16	Haemophagocytic lymphohistiocytosis	S Strobel, M Layton, J Pritchard.	King's College Hospital, ICH (London)
17	Congenital syphilis*	A Nicoll, T Lissauer	PHLS, St Mary's Hospital (London)
18	Munchausen syndrome by proxy/ non-accidental poisoning and suffocation	J R Sibert, S R Meadow, P Davis, R McClure	St James's University Hospital, University of Wales, Medical School
19	*Haemophilus influenzae* type b vaccination failure*	P Heath, M Slack, R Moxon, N Begg	PHLS, National Haemophilus Reference Laboratory
20	Vitamin K deficiency bleeding*	A McNinch, J Tripp	Royal Devon & Exeter Hospital
21	Biliary atresia	J P McKiernan, D Kelly, A Baker	Birmingham Children's Hospital, King's College Hospital
22	Medium chain acyl-CoA dehydrogenase*	R Pollitt	Sheffield Children's Hospital
22	Adverse effects of birth/delivery in water*	P Tookey, R Gilbert	ICH (London)
23	Transient & permanent neonatal diabetes	J Shield, J D Baum	ICH (Bristol)
24	Acute flaccid paralysis	N Begg	PHLS

* Studies still in progress in December 1995.

AIDS and HIV infection in childhood

Background

National surveillance of paediatric HIV infection and AIDS began in 1986 in order to monitor the incidence and prevalence of paediatric infection. It is based on a combination of paediatric, obstetric, and laboratory reporting schemes.

Most cases of paediatric HIV infection and AIDS are children born to women infected with HIV. In Europe it is estimated that 15% to 20% of babies born to HIV infected mothers and not breast fed, are infected themselves, and 25% of these develop AIDS within 12 months. With new laboratory tests, HIV infection can usually be diagnosed by 3 to 4 months of age.

Objective

The surveillance of paediatric HIV infection and AIDS in the United Kingdom and the Republic of Ireland.

Case definition

Any child less than 16 years of age who has AIDS or is HIV antibody positive, or with positive virus culture, PCR or antigen detection, or any other laboratory marker of HIV infection. Also any child born to a woman known to be HIV infected at the time of that child's birth, regardless of the child's infection status.

Study duration

The survey began in June 1986.

Analysis

By the end of January 1995 there had been 850 reports through the BPASU. Forty-seven children were infected in the course of treatment for haemophilia (15 of whom were still alive and under 16 years of age on 31 January 1995); a further 19 children were infected through blood transfusion. Five hundred and twenty-three children born to HIV infected women were reported (table 4); these included 220 children with confirmed infection, 94

whose infection status is still indeterminate, and 209 now known to be uninfected. Thirty-seven of the remaining reports are still being investigated, 110 were duplicates, and there were 114 reporting errors.

A further 544 children have been identified from other sources: 221 children with haemophilia, 15 infected through blood transfusion, and 308 children born to HIV infected women (97 with confirmed infection, 132 indeterminate, and 79 uninfected). These include reports to the United Kingdom Haemophilia Centre, reports by obstetricians to the Royal College of Obstetricians and Gynaecologists (through a reporting scheme similar to the BPASU), and reports made directly to the coordinating centre at the ICH (London), the PHLS AIDS Centre at CDSC, or SCIEH.

All reports are confidential and names are not used. Children are followed up yearly to monitor their clinical and immunological status and to determine their infection status. Children born to HIV infected women who are subsequently found not to be infected themselves are not followed up further.

Data from the various sources are combined each quarter and form the basis of the national surveillance of HIV infection and AIDS in children, which is coordinated by the ICH in association with the PHLS AIDS Centre and SCIEH. These data are used to monitor the clinical spectrum of disease in children, estimate the vertical transmission rate, and predict the future extent of vertically acquired HIV infection.

We would like to thank all members of the BPA, particularly those paediatricians who have reported cases and completed questionnaires.

Table 4 Children born to HIV infected women: reports to the BPASU to the end of January 1995

HIV infection status	Reports	Deaths*
AIDS	130	66
Other infected	90	3
Indeterminate	94	7
Uninfected	209	–
Total	523	76

* Deaths in uninfected children are excluded.

Funding

This study is funded by AVERT (AIDS Education & Research Trust). Routine collation of data each quarter and transfer to national surveillance centres is funded by the Medical Research Council.

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Reye's syndrome

Background

Surveillance of Reye's syndrome began in August 1981 as a venture shared between the BPA and CDSC. Responsibility for case ascertainment was transferred to the surveillance unit in June 1986. In the early years, the results of surveillance showed that the incidence of Reye's syndrome in the British Isles was similar to that in the United States but cases occurred at a younger mean age, there was no clear seasonal (winter) peak, no obvious association with influenza and chickenpox, and a higher case fatality rate.

In 1984/85 a study of risk factors mounted on to the surveillance database showed an association between Reye's syndrome and consumption of aspirin. In response to this and similar findings in the United States, the Committee on Safety of Medicines issued public and professional warnings in 1986 about the use of aspirin in children under 12 years. Since then, products that contain aspirin have been required to carry warning labels.

In 1991 the surveillance questionnaire was modified to collect further information about inherited metabolic disorders, because of concern that these disorders may be underrecognised. Data on the past medical history of the child, family history, and specific investigations for inherited metabolic disorders were collected over a two year period. A new simplified questionnaire was introduced at the beginning of August 1993.

Objectives

To describe the epidemiological and clinical features of Reye's syndrome in the British Isles, to monitor long term trends, and to provide a database for detailed clinical, laboratory, and aetiological studies.

Case definition

A child under 16 years old with:

- unexplained non-inflammatory encephalopathy, and *one or more* of:
- serum hepatic transaminases elevated to at least three times the upper limit of normal;
- blood ammonia elevated to at least three times the upper limit of normal;
- characteristic fatty infiltration of liver (biopsy or autopsy).

Study duration

This study began in June 1986 and is due to end in July 1996.

Analysis

Between August 1981 and July 1994 a total of 554 suspected cases of Reye's syndrome were reported to the surveillance scheme but diagnosis was subsequently revised in 136 cases (25%). Over half (64%) of the revisions were to one of the inherited metabolic disorders. In the year to July 1994, 15 reports were received and follow up was complete on 12 at the time of writing. Five of the 12 diagnoses had been subsequently revised, two cases did not meet the case definition, clarification of necropsy results were awaited on another, in one case the diagnosis was indeterminate, and in one report the onset of illness was before August 1993 and the case was allocated to the surveillance year 1992/93. Two cases were confirmed.

Confirmed cases: year to July 1994

Both cases were male and aged 3½ months and 5½ months respectively. One child lived in England, the other in Wales. One became ill in June, the other in November. One infant survived with sequelae, although no specific details were given. The outcome of the other case was unclear when the questionnaire was completed. One case had received paracetamol and amoxycillin for prodromal flu-like symptoms and gastroenteritis before admission. Both infants were investigated for inherited metabolic disorders. Details of specific investigations were not given. No abnormal results were reported.

Revised diagnosis cases

Three of the five cases were reported to have an inherited metabolic disorder: one had a possible defect of fatty acid oxidation, one possible fructose intolerance, and the third had a probable, but unspecified, inherited metabolic disorder. The ages of these three patients ranged from 3 weeks to 8.4 years (mean 34.8 months; standard deviation 57.1 months). No definitive diagnoses were made in the remaining two cases, but liver biopsy or necropsy results were considered to be inconsistent with Reye's syndrome.

Comment

The annual totals of reports to the surveillance system and confirmed cases of Reye's syndrome have fallen steadily since the peak of 93 reports (81 cases) in 1983/84. Between 1988/89 and 1991/92 the annual incidence remained moderately stable (table 5). In the

Table 5 *Reye's syndrome surveillance 1981/82–1993/94*

Reporting period (August–July)	Total reports	Revised diagnoses (inherited metabolic disorder)		Number of cases	Number of deaths (case fatality rate)	
1981/82	47	7	(3)	40	26	(65)
1982/83	69	10	(6)	59	33	(56)
1983/84	93	12	(3)	81	36	(44)
1984/85	64	8	(2)	56	32	(57)
1985/86	53	13	(4)	40	22	(55)
1986/87	47	21	(11)	26	13	(50)
1987/88	44	12	(3)	32	19	(59)
1988/89	31*	12	(6)	18	9	(50)
1989/90	24*	8	(5)	15	7	(47)
1990/91	25	12	(7)	13	5	(38)
1991/92	24†	6	(5)	16	6	(38)
1992/93	19**	10	(6)	6	2	(33)
1993/94	14§	5	(3)	2	0	(–)
Total	554	136	(64)	404	210	(52)

* Detailed information not available for 1 case. † Follow up not yet received for 2 cases. ** Follow up not received for 2 cases and 1 case did not meet the case definition. § Follow up not received for 3 cases; a further 2 did not meet the case definition; 1 case was allocated to 1992/93; detailed information unavailable for 2 cases.

past two years, however, total reports to the scheme have declined and the annual total cases of Reye's syndrome has fallen dramatically. Several factors may have contributed to these trends. Paediatricians have become more aware of inherited metabolic disorders in young children and infants. Also they are more aware of the difficulty of diagnosing Reye's syndrome in children under 5 years, because of the many disorders that mimic the syndrome in this age group. Infants reported to the scheme are likely to be more thoroughly investigated and perhaps have their diagnoses subsequently revised than was the case in earlier years. In addition, the public and professionals have been warned about the use of aspirin in children under 12 years. These factors do not appear however, to account for the fall in confirmed cases of Reye's syndrome in the two most recent surveillance years.

In an analysis of 10 years of reports to the surveillance scheme, medium chain acyl-CoA dehydrogenase deficiency (MCAD) was the inherited metabolic disorder most commonly identified in children who presented with an illness like Reye's syndrome[1]. It may be that some cases that had previously been reported as suspected Reye's syndrome have more recently been reported to the BPASU as suspected MCAD. It is proposed that cases reported as suspected MCAD whose diagnoses are subsequently revised should be reviewed for evidence of Reye's syndrome.

Reference

1. Newton L, Hall SM. Reye's syndrome in the British Isles: report for 1990/91 and the first decade of surveillance. *Communicable Disease Report* 1993;3: R11–6.

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Neonatal necrotising enterocolitis

Background

Necrotising enterocolitis is a serious gastrointestinal disease seen mainly in neonatal intensive care units. The reported mortality in established cases is between 20% and 40%.

No single aetiological factor seems to explain neonatal necrotising enterocolitis; its mucosal lesion can be provoked in several ways. It is important therefore to determine whether risk factors exist which can be avoided readily in clinical practice. Feeding policy is one such amenable factor. A prospective study carried out in five centres suggested that breast milk protects babies born prematurely from developing necrotising enterocolitis[1]. In babies fed exclusively with formula milk the incidence of confirmed disease was six to ten times greater than those fed breast milk alone, and three times greater than in those who received formula plus breast milk. Pasteurised breast milk seemed to be as protective as raw breast milk. From these data and crude estimates of the proportion of premature babies who receive no breast milk in neonatal care, it has been estimated that 500 cases of necrotising enterocolitis in Britain each year could be attributed to exclusive formula feeding. These cases would account for at least 100 deaths and 150 laparotomies.

Objective

This study was introduced to establish the incidence of necrotising enterocolitis and to determine whether early diet can influence its onset and severity.

Case definition

Grade I Cases have at least two of the following features: pneumatosis intestinalis seen on abdominal radiograph; abdominal distension, or an abdominal radiograph that shows gaseous distension or frothy appearance of bowel lumen (or both); blood in the stool; lethargy, hypotonia, or apnoeic episodes, or a combination of all three.

Grade II Cases have, as well as features of Grade I, one or more of: abdominal bleeding in response to trauma; tenderness or rigidity; mucosal tissue in the stool; abnormal bleeding in response to trauma, or spontaneous bleeding; peripheral white blood cell count below 6×10^9/l at the time of illness; peripheral platelet count below 100×10^9/l at the time of illness; or an abdominal radiograph that shows gas in the portal vein or free air in the abdomen.

Study duration

This study began in October 1993 and ended in October 1994.

Analysis

Four hundred and twenty-nine cases were reported during the 12 months of the study. Fifty reports were duplicates, 18 cases arose outside the study period, 21 were thought not to be true cases, in 28 cases identification details had not been retained, and 16 cases are still being followed up. Therefore out of the 429 initial reports, 296 actual cases remain.

Cases were confirmed if one of the following criteria was met: gas in the bowel wall or portal tract, diagnosis confirmed at surgery, diagnosis confirmed at necropsy. One hundred and fifty-two of the 296 cases were male and 144 female; 178 of the 296 cases were confirmed, 39

of which (22%) were Grade I and 139 (78%) were Grade II. Sixty-four of the 118 unconfirmed cases were Grade I (64%) and 44 Grade II (36%). The case fatality rate was 22%.

Further data are being obtained on the feeding practices of the cases reported and feeding practices in all neonatal units to determine the influence of early feeding practices on the onset and severity of neonatal necrotising enterocolitis. We expect that our findings will be presented early in 1996 and submitted for publication.

We would like to thank all the neonatologists, paediatricians, and surgeons who participated in this study.

Reference

1. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet* 1990; **336**: 1519–23.

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Congenital rubella

Background

A national programme to immunise susceptible adult women and all schoolgirls against rubella was implemented in 1970. The National Congenital Rubella Surveillance Programme (NCRSP) was established in 1971 to monitor the effect of the immunisation programme on the incidence of congenital rubella. In 1988 a combined measles, mumps, and rubella (MMR) vaccine was introduced, to be given to all children in the second year of life. This policy has had considerable success, but cases of rubella in pregnancy and congenital rubella still occur. In November 1994, as part of an attempt to avert a predicted epidemic of measles, all children aged 5 to 16 years were offered a combined measles and rubella (MR) vaccine.

Objectives

- To monitor the effectiveness of the rubella immunisation programme by determining the incidence of congenital rubella in Great Britain and investigating the circumstances of the small number of cases that still occur;
- To identify the sequelae of congenital rubella in childhood and in adult life.

Case definition

Any child up to 16 years of age who, in the opinion of the notifying paediatrician, has suspected or confirmed congenital rubella with or without defects, based on history, clinical, and/or laboratory findings.

Study duration

Congenital rubella was included in the BPASU reporting scheme in January 1990. Notifications were previously made direct to the NCRSP.

Analysis

BPASU has received 67 reports since the beginning of 1990. Thirty-five of these are confirmed cases of congenital rubella, including one child born in the Republic of Ireland and two in Northern Ireland, who are not included in the NCRSP registry figures; another three possible cases cannot be confirmed because laboratory information is lacking. Six of the confirmed cases had already been notified to the NCRSP by other sources. The 29 remaining reports included 12 duplicates, 11 reporting errors, and four for whom further information could not be obtained; two reports are still being investigated.

The NCRSP has registered 32 children with confirmed congenital rubella born since the beginning of 1990 in Great Britain, 69% of whom were first reported through the BPASU (table 6). Other sources of reports include audiologists, virologists, and CDSC.

Table 6 *Children with confirmed congenital rubella born in Great Britain, 1990–1994*

	1990	1991	1992	1993	1994	Total
BPASU	8	2	5	2	5	22
Other sources	4	1	2	1	2	10
Total	12	3	7 *	3	7	32

* Includes one set of triplets.

Altogether about 1100 individuals are registered with the NCRSP. Seventy-eight per cent have confirmed congenital rubella; the remainder do not satisfy our strict case criteria, but are registered as possible cases. Since 1988, when MMR vaccine was introduced, congenital rubella has become rare. Most of the recent reports are of infants born to mothers who were themselves born abroad and came to Britain after the age of schoolgirl immunisation. Possible ways of offering immunisation to recent immigrants should be considered.

It is essential that case ascertainment is as complete as possible, and reassuring when several clinicians report the same child. Paediatricians are encouraged to report to the BPASU all children suspected to have congenital rubella, whether or not they have the typical associated defects. We are grateful for their effort and cooperation.

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Subacute sclerosing panencephalitis

Background

Elimination of measles and its late complication, subacute sclerosing panencephalitis (SSPE) is the objective of the United Kingdom vaccination programme. Despite the introduction of measles vaccination in 1969 coverage with the single antigen vaccine was poor and the incidence of measles did not fall substantially until the measles, mumps, and rubella vaccine was introduced in October 1988 (figure 3). Consequently, a clear reduction in the incidence of SSPE has not been seen; a low plateau has been maintained in recent years.

Objective

To monitor the incidence of SSPE.

Case definition

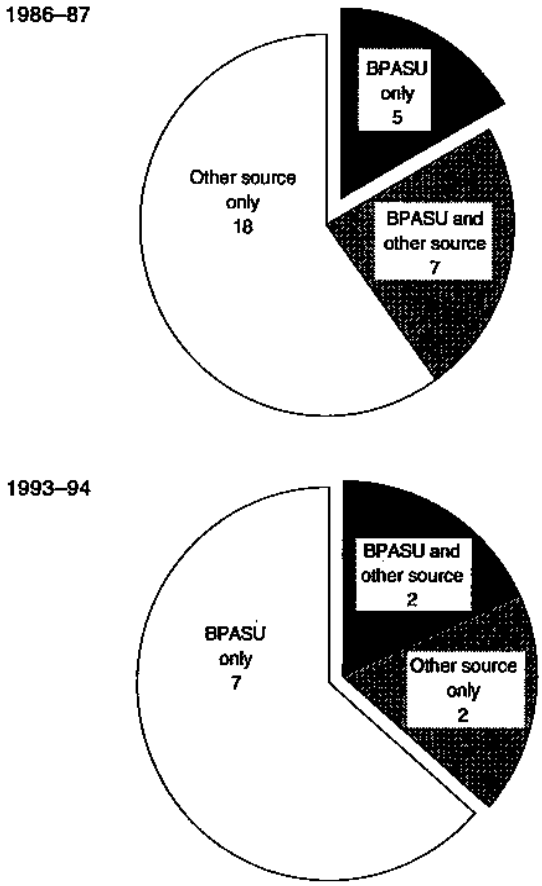
The criteria for SSPE are:

- a typical history, usually of an insidious onset of mental deterioration, followed (usually within a few months) by motor dysfunction, progressive decerebration, and death; *and*
- raised measles antibody titres in the serum and cerebrospinal fluid, typical electroencephalographic changes, and brain histology (when available).

Study duration

Cases were initially reported spontaneously to CDSC. BPASU surveillance began in June 1986 but SSPE was taken off the orange card and in July 1994. Between July 1994 and October 1995 CDSC again undertook passive surveillance. Doubts have arisen about the adequacy of passive reporting for assuring complete ascertainment (figure 3). Reporting through the BPASU was the most effective means of notification (figure 4) and unit's Executive Committee has agreed that SSPE should be placed back on the card with a request for back reports of any new cases seen in the past year.

Figure 4 Source of notifications 1986–87 and 1993–94: confirmed SSPE cases, England and Wales



Researching the aetiology of SSPE should be advanced by the new developments in genetic characterisation of measles virus strains. It is vital to ascertain all cases now that vaccine uptake is 93% and the incidence of confirmed measles in children is so low.

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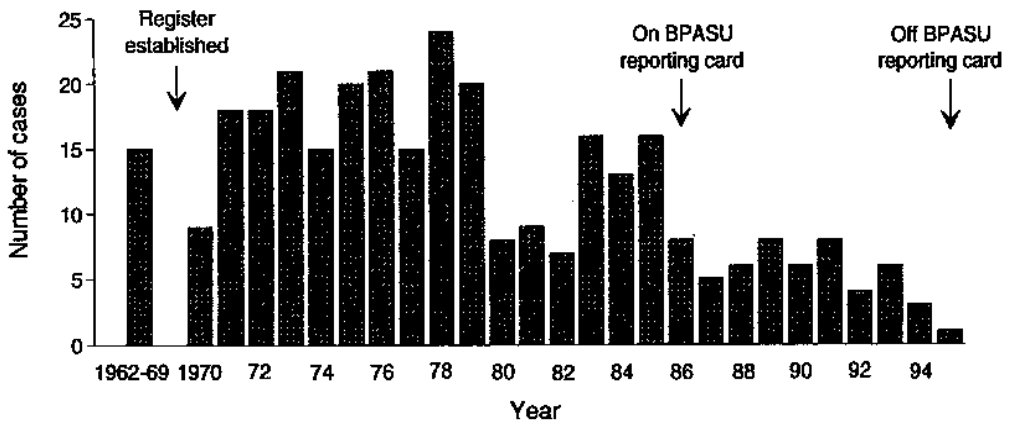
Figure 3 Cases of SSPE in England and Wales by year of onset 1962–1994



Haemophagocytic lymphohistiocytosis

Background

The term haemophagocytic lymphohistiocytosis (HLH) includes the disease that was previously known as familial erythrophagocytic lymphohistiocytosis and cases associated with infection, including virus associated haemophagocytic syndrome. The distinction was misleading; cases that are likely to have a genetic basis may not have a positive family history. Familial HLH can be triggered by infection, including infection with viruses.

Objectives

1. Establish epidemiological data in the absence of other data from the United Kingdom (only one retrospective survey has been reported, from Sweden).
2. Improve awareness and diagnosis. Although there is no diagnostic test, the syndrome is fairly easy to recognise if clinicians are of aware it.
3. Advise on management. The advent of bone marrow transplantation has made this disease potentially curable. The study coordinators have been able to advise on diagnosis and current management based on an increasing number of patient histories and contact with the reporting practitioners.
4. Research on aetiology and pathogenesis.

Case definition: clinical and laboratory criteria

- Fever for at least seven days;
- Splenomegaly;
- Cytopenia – affecting at least two of the three lineages in blood and not caused by a hypocellular/dysplastic bone marrow or malignant infiltration;
- Hypertriglyceridaemia (fasting) and/or hypofibrinogenaemia;
- Haemophagocytosis in bone marrow, spleen, lymph nodes, or other sites without evidence of malignancy.

Note: Haemophagocytic activity may not always be seen at the time of presentation and serial aspirates over a period of time may be useful.

Exclusion criteria: previous immunosuppressive therapy, concurrent malignancy, and Langerhans cell histiocytosis.

Study duration

This study began in September 1991 and ended in August 1994.

Analysis

Ninety reports were made during the three years of the survey, 54 of which have been confirmed as cases. Twenty-seven of the 90 were duplicates, 6 were reported in error or the diagnosis subsequently changed, and the diagnosis of two reported patients is not yet known. The annual incidence (18 reported cases a year) for the 36 month period was approximately 1.52 cases/million children/year. The incidence exceeds that obtained in a retrospective study in Sweden (1.2 cases/million children/year) by 27% but study design and population background are likely to explain the difference.

Treatment and outcome

Most of the patients were treated using a protocol which includes etoposide and prednisolone and more recently with dexamethasone according to a newly established international treatment protocol (HLH 1994). Cyclosporin A has been mostly used after the initial treatment intended to induce remission. Patients with severe disease who do not respond have been given antilymphocyte globulin. Severe involvement of the central nervous system at presentation seems to be a poor prognostic factor. Matched bone marrow transplantation (also recently with matched unrelated donors (MUD)) in remission has been successful in several patients.

Future research

This study has helped to establish a network of clinical and basic research. Studies are underway to identify the underlying genetic susceptibility in a subgroup of those patients and will be reported when completed.

Prospective therapeutic study

No optimal treatment of HLH currently exists, but international collaboration has led to the development of diagnostic and treatment protocols, which are being evaluated prospectively. The study coordinator is Dr David Webb, who can be contacted at the Department of Paediatrics, Llandough Hospital, Llandough, Cardiff, South Glamorgan, (telephone 01222 711711). It is important to enrol as many patients as possible, especially with the aim of assessing the overall benefits of sibling and matched bone marrow transplantation from siblings and matched unrelated donors (MUD).

Acknowledgement and thanks

The investigators would like to thank the practitioners who reported the patients and readily provided further clinical information. We are especially grateful to those who provided samples for further immunological and genetic analysis.

Continuation of voluntary reporting and advice on management

The reporting system has been very successful (as judged by the number of duplicate reports). We ask all practitioners and paediatricians to continue reporting direct to the addresses below in order to enrol patients into the therapeutic study and to help with the continuing clinical and research analysis of this still unresolved disease.

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Congenital syphilis

Background

The BPASU survey of congenital syphilis began in July 1993. Its aim is to undertake surveillance for congenital syphilis in the United Kingdom and the Republic of Ireland. The only surveillance of congenital syphilis previously was through genitourinary medicine (GUM) clinics, and it is known that not all affected or exposed children would be attending such facilities.

The importance to public health of this survey has increased since it began as suggestions have been made that antenatal screening for syphilis should cease[1]. It is thought that all women who receive antenatal care in the United Kingdom are screened for serological evidence of syphilis and other treponemal infections, such as yaws and pinta, which are serologically indistinguishable. Although national data suggest that infectious syphilis is uncommon in women in the United Kingdom, 328 new cases were reported by GUM clinics in England and Wales during the three years 1991 to 1993. Moreover, it cannot be guarenteed that the current low level of infection will be maintained. In the United States in the 1980s and 1990s, failure to provide universal antenatal care (including serological screening) has resulted in a substantial epidemic of congenital syphilis.

Objective

To determine the minimum incidence of congenital syphilis in children, detect possible maternal and other risk factors, and look for trends while the study continues.

Case definition

A confirmed case is an infant, child, or stillbirth in whom direct evidence of *Treponema pallidum* infection is found.

A **presumptive case** is **either** an infant, child, or stillbirth whose mother had untreated or inadequately treated syphilis at the time of delivery **or** an infant child or stillbirth with a reactive specific treponemal test (TPHA or FTA-Abs, **not** just VDRL or RPR) and evidence of infection.

A possible case is one treated for syphilis who does not fill confirmed or presumptive criteria.

Duration

The study began in July 1993 and will end in July 1996.

Results

Twelve reports were made in the first two years of the survey – six in 1993, three in 1994, and three so far in 1995. One report in 1993 was not confirmed as a case when further information became available. Further information is awaited about three reports (one from 1994, two from 1995). Of the eight confirmed cases, one was "presumptive" (1993) and seven were "possible" (four from 1993, two from 1994, one from 1995). All cases came to medical attention through maternal screening. All the mothers had evidence of previous infection with syphilis, for which they had been treated. The small number may be explained in four ways: there may be no cases to diagnose and report, there may be a failure to make the diagnosis (especially in "possible" cases without symptoms), diagnosed cases may not be reported, and diagnosed cases may not see paediatricians (it is known that some are referred to GUM physicians with their mothers).

The research team is investigating the small numbers through the BPASU scheme to see if this could represent underascertainment or underreporting. In addition, a group of GUM physicians in the United Kingdom called the British Cooperative Clinical Group (BCCG), has begun a reporting scheme analogous to the BPASU scheme, but using quarterly reports. The BCCG is also looking for cases of treponemal infection (including syphilis) requiring treatment in pregnant women, which will help to show how many infections are being detected by antenatal screening. Routine quarterly reporting of all cases of treponemal infection to the six PHLS reference laboratories began late in 1994. It is planned that laboratory reporting will form the basis of long term surveillance. The data from these surveys and laboratory reporting will form the basis of a cost benefit and policy analysis of the value of antenatal screening for syphilis.

Reference

1. Nicoll A, Moisley C. Antenatal screening for syphilis. *BMJ* 1994; **304:** 1253–4.

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Alleged Munchausen syndrome by proxy/non-accidental poisoning and suffocation

Background

The term "Munchausen syndrome by proxy" was first used in 1977 to describe illness or disability in a child, which is fabricated by another person (usually the mother) and causes the child to be presented persistently to doctors. The "illness" goes when the child is separated from the perpetrator. The more serious forms of such abuse include non-accidental poisoning and suffocation. These last two types may also occur in isolation.

There has been no epidemiological survey to date of Munchausen syndrome by proxy, non-accidental poisoning or non-accidental suffocation. The BPASU study aims to define both the incidence and epidemiology of Munchausen syndrome by proxy and identify its commonest forms. Previous research has shown that half the children so abused also suffer from another form of abuse. It is not known what proportion of children suffer Munchausen syndrome by proxy solely through the parent inventing false stories, rather than through direct harm by way of poisoning, suffocation, or other physical injury.

Non-accidental poisoning and suffocation of children are uncommon forms of child abuse, and little is known about whether they are isolated events or simply one aspect of more continuing child abuse, including factitious illness and Munchausen syndrome by proxy. Non-accidental suffocation is a recognised feature of Munchausen syndrome by proxy and accounts for a small minority of "cot deaths". Suffocation of children outside this context has not been well documented.

Objectives

To define the incidence and epidemiology of Munchausen syndrome by proxy, non-accidental poisoning, and suffocation and to compare management and outcome of the different types of abuse.

Case definition

Any child under 16 years of age, for whom a child protection conference has been convened because of suspected:

- *Munchausen syndrome by proxy*: "An infant or child aged 16 years or under, presented to doctors with disability or illness fabricated by an adult"
- *Non-accidental poisoning*: "An infant or child aged 16 years or under who has been deliberately poisoned (using an agent by any route) by an adult"
- *Non-accidental suffocation*: "Deliberate suffocation or asphyxiation of an infant or a child under the age of 16 years by an adult"

Any of the above alone, or in combination, should be reported.

Aims

The purposes of this survey are:

1. To describe the epidemiology of child abuse taking the form of Munchausen syndrome by proxy (including those cases involving non-accidental poisoning and suffocation); assess the incidence in relation to the different grades of abuse, which are as follows: false illness story; false illness story with fabrication of signs; false illness story with physical abuse of child by perpetrator; false illness with poisoning or suffocation.
2. To assess the epidemiology of non-accidental poisoning or suffocation alone.
3. To analyse the different types of abuse in relation to their presentation, management, and outcome.

Method

After a report was received through the BPASU a brief questionnaire was sent to the reporting paediatrician. No direct contact was made with the general practitioner, patient, or family. It is planned that a second questionnaire will be sent to obtain data on the longer term outcome of the child.

Study duration

The study began in September 1992 and ended in August 1994.

Results and discussion

Case reporting has now been completed. The findings relating to the major points in our study were presented at the BPA's annual meeting in York in March 1995. Detailed results are still being analysed and will be published soon.

This study will produce valuable information about the epidemiology of these three forms of child abuse. It has depended upon the collaboration and efforts of reporting paediatricians. To these paediatricians, and all others who have helped in this study, we are most grateful.

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Invasive Haemophilus influenzae *infection following Hib immunisation*

Background

Before immunisation was introduced in the United Kingdom (UK) it was estimated that over than 1300 infants and young children suffered an episode of invasive *Haemophilus influenzae* type b (Hib) disease every year. This included more than 900 cases of meningitis. It was estimated that over 60 children died of this infection each year and that over 100 were left with a neurological disability.

The BPASU included invasive *H. influenzae* infection following Hib immunisation in its reporting system in September 1992, when Hib conjugate vaccines became part of the vaccination schedule in the UK and the Republic of Ireland. It was important to establish a surveillance mechanism that would detect children who developed invasive Hib disease after immunisation.

Children are immunised at 2, 3, and 4 months of age in the UK and 2, 3, and 6 months of age in Ireland. The duration of protection provided by the schedule is not known, but it is hoped that it is sufficient to avoid the need for booster immunisation in the second year of life, which is given in most other western countries. It is particularly important therefore to maintain surveillance in children as they get older.

Objectives

To identify cases of:

1. Hib disease occurring in children who have been vaccinated and thereby to estimate the efficacy of Hib conjugate vaccines in British and Irish children; in cases of vaccine failure to document host factors that might be relevant, the clinical presentation of disease, and the acute and convalescent concentrations of Hib antibody.
2. Invasive disease in vaccinated children caused by *H. influenzae* not of type b – that is, cases not preventable by Hib vaccine.

Paediatricians are asked to report cases immediately, preferably by telephone, if *H. influenzae* is isolated from a normally sterile site from a child under 10 years of age who has received at least one dose of Hib vaccine, irrespective of the interval between vaccination and disease. Attempts are made to collect acute and convalescent specimens of serum and the strain of *H. influenzae* is sent to the PHLS National Haemophilus Reference Laboratory at the John Radcliffe Hospital, Oxford where its serotype is confirmed by standard microbiological techniques and capsular genotyping is undertaken using a method based on the polymerase chain reaction.

Case definition

True failure of the vaccine is defined as the occurrence of invasive Hib disease after three doses of vaccine, or more than one week after two doses given in the first year of life, or more than two weeks after a single dose given to a child over 12 months of age. Hib disease that occurs after vaccination has been given but before protection could reasonably be expected to develop constitutes an apparent failure of vaccine – for example, Hib disease after one dose in the first year of life.

Study duration

This study began in September 1992; an end date has yet to be set.

Analysis

By 1 April 1995, 147 initial reports had been made: 57 were from paediatricians, 60 from microbiologists, 29 from public health physicians, and one other. Thirty-five represented true vaccine failures, 53 were apparent vaccine failures, 23 were cases of invasive disease due to non-capsulated strains of *H. influenzae*, and eight cases were due to non b capsulated strains. Three possible cases were reported (protective course of vaccination received, isolate of *H. influenzae* obtained but not typed) and 25 reports did not meet the case criteria. Reports have come from England (117), the Republic of Ireland (21), Northern Ireland (5), Scotland (3), and Wales (1).

Twenty-nine of the 35 true vaccine failures were vaccinated at less than 12 months of age (the remaining six were older than 12 months), and 23 had received three doses of vaccine (20 by 6 months of age). The efficacy of three doses of vaccine by 12 months of age is

Table 7 *Hib vaccine failures*

Presenting illness		Associated conditions (clinical)		Associated conditions (laboratory)	
Meningitis	20	Prematurity	6	Immunoglobulin deficiency	15
Epiglottitis	7	Chromosomal abnormality (three Down's syndrome)	4	(ten IgG2 deficiency; includes seven with clinical factor)	
Pneumonia	4	Dysmorphic and developmental delay	2		
Bacteraemia	2				
Orbital cellulitis	1				
Septic arthritis	1				

estimated to be 99.3% (95% confidence interval 98.3–99.8%).

Convalescent specimens were available for serological testing in 32 of the 35 cases of true vaccine failure and a poor antibody response to disease (<1 μg/ml) was noted in 15, seven of whom had an associated condition. Seven have now received a booster dose and five have developed a protective antibody concentration.

Thirty-one cases of invasive disease due to non type b *H. influenzae* have been recorded. During 1994, an isolate reported from a fully immunised child was as likely to be a strain of *H. influenzae* other than type b as it was to be *H. influenzae* type b.

Comment

The surveillance for Hib vaccine failures has confirmed the excellent protective efficacy of Hib conjugate vaccines for the first year of life. Furthermore, it has highlighted children who develop invasive disease despite vaccination as a special group worthy of further immunological evaluation and careful follow up.

The persistence of protection provided by primary immunisation without a booster must continue to be carefully monitored in the UK and Ireland and surveillance for vaccine failure remains the best means of doing this. Verification of isolates in such cases is vital, particularly as non b *H. influenzae* becomes a relatively more important cause of invasive disease. Early reporting by telephone enables appropriate specimens to be collected for the isolate to be characterised. It also enables paediatricians to receive prompt feedback.

We are most grateful for the collaboration of paediatricians and microbiologists in this study.

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Vitamin K deficiency bleeding

Background

One of the first conditions to be studied through the BPASU network was vitamin K deficiency bleeding, which was then known as "haemorrhagic disease of the newborn". The new term is now preferred as it is more informative and does not imply misleadingly that the condition is confined to newborn babies. The BPASU survey found 25 confirmed and two probable cases in the British Isles in the two year period from March 1988 to February 1990[1]. At that time at least 60% of newborn babies received prophylaxis with intramuscular vitamin K and 13% received no prophylaxis. Twenty of the 27 cases reported had received no prophylaxis, seven had received a single oral dose of vitamin K (Konakion (Roche)) at birth, and no cases had received intramuscular prophylaxis.

The trend towards oral rather than intramuscular prophylaxis was encouraged by reports[2,3] suggesting that intramuscular vitamin K might double the risk of subsequent malignancy. Subsequent studies have failed to confirm such a risk[4] but in 1993 a national survey of prophylaxis policies (John Barton and colleagues, unpublished observations) showed that 60% of babies were receiving oral prophylaxis, 35% intramuscular prophylaxis, and 5% none. Most maternity units that used oral prophylaxis routinely offered multiple doses as recommended by a working party of the BPA[5]. The rationale for repeated oral doses is that when bleeding occurs after a single oral dose at birth its onset is at least delayed, and doses repeated at intervals should therefore "repeatedly delay" the onset of bleeding throughout the period of risk.

A second BPASU survey of vitamin K deficiency bleeding began in January 1993 to monitor the efficacy of current prophylaxis regimens.

Objective

To re-evaluate the incidence and epidemiology of vitamin K deficiency bleeding.

Case definition

Any infant under 6 months of age with spontaneous bruising, bleeding, or intracranial haemorrhage associated with prolonged clotting times, not due to an inherited coagulopathy or disseminated intravascular coagulation.

Study duration

The study began in January 1993 and ended in December 1994.

Analysis

Up to December 1994, 17 probable or confirmed cases had been reported. Five of the eight babies who bled in spite of oral prophylaxis had liver disease and one was failing to thrive because of pancreatic dysfunction, one

baby had normal liver function, and another was not tested. Six babies received a single dose of oral vitamin K at birth: five cases received a 1 mg dose; the dose for one was not specified. One baby received 2 mg on both the first and second days of life and bled at 46 days. One baby with anti-trypsin deficiency presented at 42 days with an intracranial haemorrhage, but the initial dose is not known, nor whether repeat doses were given. Further details of these cases were published in the 1993 BPASU Annual Report. The full results of the survey are being prepared for publication and will be described in future BPASU reports.

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Biliary atresia

Background

Biliary atresia is an uncommon disease of infancy, which is fatal if not treated. It is the commonest cause of liver disease in children of such severity as to require liver transplantation. The aetiology and incidence of the condition in the United Kingdom and the Republic of Ireland are unknown.

Objectives

The BPASU survey seeks to answer the following questions. What is the national incidence of biliary atresia? Are there any recognisable aetiological features? What is the current pattern of referral and why is referral delayed? What is the outcome for affected children following modern management and how many will eventually need liver transplants?

Study duration

This study began in March 1993 and ended in February 1995.

Analysis

More than 80 cases have been confirmed and a number await confirmation. A number of duplicate reports were made, confirming that the scheme provides comprehensive coverage. Two cases have been identified by other means and not through the BPASU. Paediatricians who are likely to have seen children with liver disease are being contacted, reminding them that the study has come to an end, and asking for information about any children with biliary atresia who may not have been reported.

The mean age at which children with biliary atresia undergo surgery has fallen to 59 days. In many cases, however, there remains an unacceptable delay and in three cases children were referred too late for surgery to be appropriate. It is disappointing to note that, for a rare condition, surgery is still being carried at a large number of centres. Eleven centres have operated on children with biliary atresia in the past two years, but only three of these centres saw more than two children a year.

The first part of the study is now complete: the recognition of a cohort of patients for the database. The next part of the study is to follow the progress of these children. This will be the subject of further reports. When the cases have been confirmed a more comprehensive report with detailed analysis will be published.

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Medium chain acyl-CoA dehydrogenase deficiency

Background

This is an inborn error of fatty acid oxidation whose presentation varies. Some patients develop hypoketotic hypoglycaemia or an acute encephalopathy (similar to Reye's syndrome), whereas others may present with hypotonia, hepatic dysfunction, or remain asymptomatic. The sudden and unexpected death of some may be attributed to sudden infant death syndrome. Studies of the frequency of the common mutation in heterozygotes suggest that medium chain acyl-CoA dehydrogenase (MCAD) deficiency is relatively common, with a birth prevalence of about one in 10000. It seems, however, that fewer than a half of these are diagnosed clinically.

Objectives

To identify all patients in the United Kingdom and the Republic of Ireland diagnosed during the period of the study. To provide data in order to make informed decisions about whether to include MCAD deficiency in a neonatal screening programme. It is hoped that the management of individual patients and their families will benefit.

Case definition

Through an accepted laboratory criterion.

Study duration

The study began in March 1994 and is due to end in February 1996.

Analysis

Fifty-three returns were made during the first year of the study, identifying 30 newly diagnosed patients in 27 families. Most of the discrepancy between the number of returns and the number of patients was due to multiple reporting, reflecting the tendency for such patients to be referred on to specialist centres either before or after diagnosis.

Seven of the cases had a family history. Two of the new cases were babies born into families where MCAD deficiency had been diagnosed in an older sibling. A third case was investigated because an older sibling had died of Reye's syndrome. In one family an older sibling, in one a twin, and in one a younger sibling of newly diagnosed cases of MCAD deficiency were also diagnosed with the condition, although as yet without clear symptoms. A further child, born into a family known to be at risk, was erroneously diagnosed as unaffected shortly after birth but then had a hypoglycaemic episode at 1 year of age.

The age at diagnosis in the 23 index cases without family histories ranged from 2 days (fortuitously in the course of another investigation) to 14 years. In four cases the initial attack was fatal and four others were left with some degree of neurological impairment. Twelve patients were diagnosed promptly after the first crisis and survived without evidence of neurological damage. The current picture of this disorder in the United Kingdom is slightly less gloomy than that from an earlier international survey[1], but the morbidity and mortality are substantial with a death attributed to MCAD deficiency in seven of the 27 affected families. The numbers involved are too small to draw definite conclusions but the geographical distribution of diagnosed cases appears to be uneven. This may be due to regional differences in gene frequency, the natural history of the disorder, or the proportion of symptomatic cases diagnosed[2].

Further work

Data collection through the BPASU will continue for a further year. Selected diagnostic laboratories will be approached separately in order to consolidate the data and check diagnostic information that is missing or ambiguous in the current returns.

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Adverse neonatal outcomes of delivery or labour in water

Background

A survey by the National Perinatal Epidemiology Unit undertaken in 1993 found that facilities for women to labour and/or give birth in water are widely available[1]. Altogether, about 4500 women gave birth in water in 1992 and 1993 in England and Wales and a further 8000 women were reported to have laboured in a birthing pool, but got out for delivery. Adverse outcomes are rare in the low risk women likely to use such facilities, but there have been a handful of reports of perinatal death or damage following, but not necessarily attributable to, labour and/or delivery in water.

Objectives

1. To estimate the incidence of adverse neonatal outcomes in babies delivered in water;
2. To identify babies who are admitted to special care units or die following labour in water and to examine whether there is evidence that the use of water during labour is associated with adverse outcome.

Case definition

Following delivery or labour in water:

- any perinatal death; and
- any admission to special care unit within 48 hours of birth.

Study duration

The study began in April 1994 and will continue for two years.

Analysis

The incidence of adverse neonatal outcomes in babies delivered in water will be estimated (the denominator will be derived from a separate survey by the National Perinatal Epidemiology Unit). Appropriate comparison rates for low risk pregnancies do not currently exist and will be determined from existing sources of data. No estimate of the incidence will be made for adverse outcomes following labour only in water, but all cases will be scrutinised for clues about risk factors and mechanisms.

By the end of May 1995, 39 returns had been made through the BPASU. Twenty-eight of these satisfied the case definition, seven were duplicate reports, two were errors, and one was still being investigated. One additional case was reported direct to the investigators. About two thirds of the returns are of deliveries in water, one third of labours only. Reporting paediatricians are sent a form requesting antenatal and paediatric details. It is planned that follow up information about babies who were admitted to special care units will be sought in their second year of life from the reporting paediatrician.

The investigators are collaborating closely with the National Perinatal Epidemiology Unit in Oxford. We are very grateful for the cooperation of reporting paediatricians and thank them and their colleagues in midwifery for reporting cases and completing study questionnaires.

Funding

The study is funded by the Department of Health.

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Transient and permanent neonatal diabetes

Background

Transient neonatal diabetes is a very rare condition that affects babies born at term. Failure of beta cell maturation has been proposed as the underlying pathology. It was recently proposed that imprinting of an "insulin gene" may be important in its aetiopathogenesis[1]. Imprinting refers to the differential expression of developmental genes depending on which parent the genes are from[2]. It is supposed that an abnormality in an imprinted gene or genes in fetal life leads to diabetes that presents soon after birth but later resolves as the gene or genes from the other parent which were inactive in utero are activated.

Objective

The study was designed to establish the incidence of both transient and permanent forms of neonatal diabetes. It was also hoped that the study would define the clinical, physiological, and genetic characteristics of these conditions.

Case definitions

- *Neonatal onset diabetes*: all infants of 37 weeks gestation or older who develop persistent hyperglycaemia requiring insulin treatment within the first 6 weeks after birth.
- *Transient neonatal onset diabetes*: those who become non-dependent on exogeneous insulin within the first year of life.
- *Permanent neonatal onset diabetes*: those who still require insulin treatment at the age of 1 year (and, by inference, permanently thereafter).

Study duration

The study commenced in July 1994 and ended in August 1995.

Analysis

Two cases of neonatal diabetes at term were reported during the study, giving an incidence of one per 400 000 births. One patient died at 3 days of age and the other has developed classical transient neonatal diabetes. A further 12 cases of older children and adults with a previous history of transient neonatal diabetes have been reported to the study coordinators. These cases have provided additional genetic material for analysis.

The most significant finding to have originated from this study is of uniparental isodisomy (the inheritance

of both chromosomes from a single parent: in these cases from the father) of chromosome 6 in two cases of true transient neonatal diabetes. Both transient neonatal diabetes and uniparental isodisomy of chromosome 6 are very rare findings and the occurrence of both in two unrelated cases indicates causal association. We have recently published work suggesting that a gene on chromosome 6 that may be responsible for normal pancreatic growth and development is maternally imprinted in fetal life and that the two cases with paternal isodisomy were diabetic because this imprinted maternal gene was absent. The resolution of the diabetes was due to either the paternal gene(s) or gene(s) at a different locus being activated postnatally[3]. This condition is so rare that we are still awaiting the first live, term infant with neonatal diabetes in order to study the dynamic physiology of the acute neonatal condition. In order to increase the chances of recruiting acute cases we hope to extend the survey to the Dutch and possible German surveillance units and are currently discussing the practicalities of this proposal with our European colleagues.

Funding

This study was financed through a small grant award from the British Diabetic Association. A further grant from the British Diabetic Association has been awarded to Dr J Shield in association with Drs I K Temple and P A Whittaker (Southampton) and Dr D O Robinson (Salisbury) to study submicroscopic deletions in chromosome 6 around a potential candidate gene site (the insulin-like growth factor 2 receptor gene).

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Acute flaccid paralysis

Background

For a nation to gain a certificate of poliovirus eradication as part of the World Health Organisation's commitment to global eradication of polio by the year 2000, active clinical surveillance of suspected "wild" polio must be undertaken. In practical terms, this means being able to detect and investigate all cases of acute flaccid paralysis in children. There was a strong case for the establishment of a scheme in the United Kingdom and the Republic of Ireland. Although paralytic polio is a notifiable disease, fewer than a half of all cases diagnosed in England and Wales between 1985 and 1990 were notified. Some cases were not detected until months, and occasionally years, after the acute illness. A request was made for all cases of acute flaccid paralysis to be reported, not only those in which polio was suspected.

Objectives

To measure the annual incidence of acute flaccid paralysis in children, and to determine its clinical features and whether the illness is caused by polio virus infection. If so, is the "wild" or vaccine-like virus responsible?

Case definition

In a child up to 16 years, acute onset of flaccid paralysis in one or more limbs or acute onset of bulbar paralysis. The differential diagnosis of acute flaccid paralysis includes paralytic polio, Guillain-Barré syndrome, transverse myelitis, and traumatic neuritis.

Study duration

This study began in July 1991 and ended in June 1994.

Analysis

Cases were reported to the investigator by telephone in the first instance, to initiate timely laboratory investigations. The single most important investigation is viral culture of faeces and at least two specimens, taken 24 to 48 hours apart and within a week of onset of paralysis, were requested.

One hundred and twenty cases were reported but only four cases of paralytic poliomyelitis were detected. Three were recipients of vaccine and the fourth case was an unvaccinated child who acquired the infection in India. No indigenous cases due to wild poliovirus were reported. Of the remaining cases, 68 were diagnosed as Guillain-Barré syndrome, 37 had other miscellaneous diagnoses, and in 11 cases the diagnosis was not known.

Surveillance was maintained until July 1994. Several other countries have followed the BPASU initiative by establishing surveillance of acute flaccid paralysis. The newly formed British Neurological Surveillance Unit has included acute flaccid paralysis in adults as one of its reportable conditions.

Acute flaccid paralysis is no longer included in the BPASU scheme, but paediatricians are asked to investigate all cases that fulfil the case definition above by the submission of at least two stool specimens for virological examination (taken 24 to 48 hours apart and within a week of the onset of paralysis).

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8 New studies in 1995

Three new studies have been introduced in 1995. They are as follows:

Pyridoxine dependency

Background

Pyridoxine dependency is a rare, treatable, recessively inherited cause of seizures that start in early childhood. It was first identified in 1954, when intractable seizures in a neonate were found to respond to a vitamin preparation. Further analysis showed that pyridoxine was responsible for the improvement. Since 1954 fewer than 50 definite cases have been described, all in case reports or small hospital based series. No large scale or population based study has ever been reported and the incidence and prevalence are unknown. Up to a third of reported cases present atypically with – for example, an onset of convulsions later than the neonatal period or a transient response to standard anticonvulsants. Other clinical complications occur, such as abdominal symptoms, early visual agnosia, structural changes in the central nervous system, or seizures provoked by intercurrent febrile illnesses, but their frequency is unknown. The condition may be under recognised. The outcome for psychomotor development is reputed to be poor even in cases that are treated early, but this is debatable as no formal study has been undertaken. Daily dosages of pyridoxine for individual patients of between 10 mg and 1000 mg daily have been reported, but the dose is not usually changed with age and the optimal dose is unknown. Individual case reports suggest that a disorder of gamma amino butyric acid metabolism may be the cause but neither a metabolic nor a genetic abnormality has been identified.

Objectives

This study will:

1. determine the prevalence of definite or possible pyridoxine dependent seizures in children under 16 years of age.
2. prospectively study the incidence in children under 5 years of age.
3. define the clinical presentation, natural history, and clinical management of pyridoxine dependency.

Case definition

Pyridoxine dependent seizures: recurrent seizures that respond to pyridoxine, or any child receiving pyridoxine for suspected pyridoxine dependency.

Definite cases will be defined as neonates, infants, or young children with recurrent (that is, two or more) seizures of any type, including infantile spasms, that cease within seven days of the administration of oral pyridoxine (usual dose: 30 mg/kg/day, range 15 mg to 1000 mg/day) or within 30 minutes of intravenous pyridoxine (usual dose 100 mg, minimum 50 mg), that recur when pyridoxine supplementation is withdrawn, and that cease again when pyridoxine is given as above. Possible cases will be defined as above, but without an attempt to withdraw pyridoxine.

Study duration

September 1995 to October 1996.

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Cerebral oedema following diabetic ketoacidosis

Background

Cerebral oedema is a devastating complication of diabetic ketoacidosis in children, and appears to be sporadic and unpredictable. The most recent figures available show that between 10 and 20 children under 19 years of age die each year from diabetic ketoacidosis in Britain. In a large American study conducted over 25 years half of the deaths associated with diabetic ketoacidosis could be attributed to cerebral oedema, but other causes of death associated with diabetic ketoacidosis may now be much less common. The incidence of cerebral oedema in Britain is unknown.

The aetiology of cerebral oedema during treatment for diabetic ketoacidosis is not understood and, even when managed optimally by current standards, cases still occur. Retrospective studies suggest that cerebral oedema is commoner in newly diagnosed diabetes, especially in children under 5 years of age. It was thought initially that the postmortem changes might have resulted from cerebral anoxia due to reduced blood volume and haemoconcentration. Other contributory factors in the development of cerebral oedema may be hypoxia that results from rapid infusion of bicarbonate, a high initial concentration of glucose in plasma, the rate and/or quantity of intravenous fluid administration, and a fall in plasma sodium concentration. Animal studies have suggested that insulin itself is required for the development of cerebral oedema. There have been no sizeable case control studies to support any of these hypotheses.

This study will compare the clinical course of cases of cerebral oedema with controls who develop diabetic ketoacidosis but without cerebral oedema, ascertained by a separate reporting mechanism, which we will

develop. This will be the first large case control study in this important area of research. The study will also investigate the outcome of cerebral oedema in the UK.

Objectives:

1. To analyse all deaths attributable to diabetic ketoacidosis, and all cases of cerebral oedema (whether fatal or not).
2. To establish an independent national procedure for the ascertainment of cases of diabetic ketoacidosis in the childhood population.
3. To estimate the absolute risk of cerebral oedema among children with diabetic ketoacidosis.
4. To identify factors in the clinical presentation and subsequent clinical course of the child with diabetic ketoacidosis that may influence the development of cerebral oedema.
5. To study the outcome of cerebral oedema in Britain in terms of mortality and morbidity.

Case definition

1. Sudden or unexpected deterioration in conscious level in a child with diabetic ketoacidosis.
2. Any death during assessment or management of diabetic ketoacidosis.

Study duration

October 1995 to November 1996, extension subject to review.

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Congenital cataract

Background

Despite considerable recent progress in the surgical and optical management of congenital and infantile cataract, a significant proportion of treated children continue to be registered blind (up to 30% in the United States of America). Congenital and infantile cataract can also cause mild or moderate visual impairment, which may go unrecognised, particularly if unilateral. In children with multiple disabilities, it may be the most readily treatable eye disorder and the improved vision that results from treatment may contribute to the child's overall development.

Early detection and treatment of congenital and infantile cataract is probably the most important of a number of factors relevant to good visual outcome. In humans the 'critical period' during which interventions to prevent the development of irreversible amblyopia are likely to be most successful is from birth to 10 weeks of age. The best reported visual outcomes are in children who undergo surgery early within this period. Early surgical intervention requires detection and ophthalmic referral in the neonatal period. Children not identified by specific neonatal examination will present at different ages and to various health professionals, depending on the severity of visual loss and the presence or absence of other ocular or systemic disorders. The current patterns of presentation and detection in the United Kingdom, including the age at presentation, to whom the child first presented, and the reason for first presentation are not known.

Epidemiological data on congenital and infantile cataract are important to the development of effective recommendations about its early detection and ophthalmic management. The main sources of data on congenital and infantile cataract in the United Kingdom are registers of partial sight and blindness, a few surveys of children attending schools for the blind, and clinical case series. All these sources are limited in terms of completeness, potential bias, or detail and most studies based on them have been retrospective. Hospital data suggest ophthalmologists in the United Kingdom see about 150 new cases each year but the birth prevalence is not known.

Numerous causes of congenital and infantile cataract have been reported but it is not known if the underlying cause is associated with the patterns of detection or of ophthalmic referral. Surgical and optical treatment techniques for congenital and infantile cataract have advanced in recent years but there are no uniform treatment policies for either unilateral or bilateral cases. Different centres have reported the results of their management regimens. Many reports involve small numbers of patients and provide limited data.

Research questions

1. To estimate the birth prevalence of congenital and infantile cataract in the British Isles.
2. To determine the national and regional patterns of presentation and ophthalmic referral.
3. To assess aetiology in incident cases and to determine the proportion attributable to preventable causes.
4. To determine the factors associated with good visual outcome.

Case definition

Any child under 16 years of age who has suspected or confirmed cataract(s), which may be unilateral or bilateral and of any severity. This includes any child who has been treated for cataract(s) in the past four weeks.

Study duration

The study began in October 1995 and will continue until October 1996.

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9 Past studies revisited

Drowning and near drowning in children

Drowning and near drowning is an important cause of death and disability in children in many parts of the world. In Britain about 70 children drown each year with only road traffic accidents and thermal injury being commoner causes of accidental death. Until 1988, however, the problem of drowning and near drowning in Britain had received little attention. We therefore studied this problem using the BPASU. Our study examined several areas: basic epidemiology and prevention, the outcome for children who nearly drown, epilepsy and drowning, and child abuse and drowning.

Basic epidemiology and prevention[1]

We found that substantial numbers of children under 5 years of age drowned or nearly drowned when given access to water, particularly in garden ponds and domestic swimming pools. The use of fencing and other environmental measures has been successful in Australia. Very few children drowned in supervised situations, such as municipal pools. Only one child died in each year of our study in swimming pools supervised under the Health and Safety Regulations. A substantial number of older children drowned in unsupervised swimming situations, such as rivers, lakes, and in the sea.

Progress since study

The publication of our study's results aroused considerable media and professional interest. We held a conference to look at the problem of prevention, and formed an alliance with the Royal Life Saving Society (RLSS). This resulted in joint work to prevent unsupervised swimming and to provide barriers to water. We have ensured that advice about safety of toddlers near water is part of the child health surveillance programme, but legislation is unlikely in the present political climate. Together with the RLSS we continue surveillance of drowning deaths and would like an opportunity to study near drowning again through the BPASU.

The outcome for children who nearly drown[2]

We found that all 52 children unconscious with normally reacting pupils made a complete recovery. Thirteen of 29 children who were unconscious with fixed dilated pupils died, eight were profoundly handicapped, and eight survived normally. None of the children who made a normal recovery were still unconscious after 24 hours.

Epilepsy and drowning[3]

In our study of the risks of swimming for children with epilepsy no child with epilepsy drowned while swimming under supervision.

Child abuse and drowning[4]

We became aware during our study that a number of children were deliberately immersed by adults. We showed that non-accidental bath drowning does occur and that drowning in the bath over the age of 2 years is likely to be due to abuse.

We hope that the results of our studies have been of value our colleagues.

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Haemorrhagic shock encephalopathy syndrome

The term "haemorrhagic shock encephalopathy syndrome" was introduced in 1983 to describe a rare but devastating multisystem disorder of young children[1]. The main features of the disease, which usually strikes in the first year of life, are acute onset of encephalopathy, shock, a bleeding tendency, diarrhoea, falling haemoglobin and platelet counts, acidosis, raised hepatocellular enzymes and impairment of renal function, with negative cultures of blood and cerebrospinal fluid. Many affected babies die and survivors are often brain damaged. The BPA and CDSC set up a surveillance system in 1982 to monitor cases throughout the British Isles because it was thought that the disorder might be caused by a new enviromental agent. From 1986 to 1988 cases were ascertained through the active reporting scheme of the BPASU. The second phase of the surveillance was supplemented by examination of the case notes, which were kindly made available by the reporting clinicians. Reports were subsequently published[2,3].

In addition to the diagnostic criteria originally suggested, the cases in the survey often also displayed rapid, shallow, or irregular breathing, progressive enlargement of the liver, neutrophil leucocytosis; moderate hypernatraemia, hypoglycaemia (sometimes profound); and mild hyperammonaemia. Coma and convulsions occurred in all. Severe encephalopathy was demonstrated by abnormalities on electro-encephalography, cranial ultrasonography, and computed tomography, and at necropsy by cerebral oedema, sometimes with herniation. Fatty change was sometimes found in the liver, but no pathognomonic histological features were identified in any tissue.

Ninety-six cases were reported from 1982 to 1988 that satisfied the diagnostic criteria (table 8). There was no clustering of cases and only a slight preponderance of cases in the winter months. Nearly all the babies were found seriously ill in the morning, after having been put to bed healthy or mildly unwell. Males outnumbered females by 1.3 to 1. Ninety-two per cent of patients were under 1 year of age, the modal age being 13 weeks. A few cases were reported in older children, the oldest being 15 years; several of these older children had pre-existing neurodevelopmental problems. Forty-six of the 79 patients for whom outcome data were available died, 27 survived with neurological impairment, and only 6 appeared to have made a full recovery.

Extensive microbiological investigations yielded no consistent bacterial or viral pathogen. This, together with the absence of clustering, makes it unlikely that one specific organism was the main cause of the illness, but the majority of patients had varying symptoms of minor prodromal infection and were febrile at presentation. Some had a temperature of over 41°C and were soaked in sweat.

Haemorrhagic shock encephalopathy syndrome has several features in common with Reye's syndrome. Reye's syndrome, however, typically affects older children and has a slower onset, vomiting is prominent, diarrhoea or bleeding tendency do not occur, and there are different ultrastructural changes in the liver.

It was concluded that haemorrhagic shock encephalopathy syndrome is a distinct clinical entity. Although the diagnostic term had only recently been introduced, a new environmental agent was unlikely, and the disease did not appear to be on the increase. The cause of the disease remains unknown. It is difficult to distinguish between the primary disorder and the various secondary metabolic disturbances. It was suggested that the title "haemorrhagic shock" is misleading in that it implies that shock ensues from haemorrhage rather than preceding it. The survey identified no treatment of definite benefit, but it was suggested that measures to control cerebral oedema should be given priority since this appeared to be the most damaging feature of the syndrome.

Several authors have proposed that haemorrhagic shock encephalopathy syndrome may in fact be the same as heat stroke, pointing to the similarity of the clinical and pathological features, and to the high temperatures exhibited by many cases. Although the disease is rare, its devastating effects call for continuing studies to determine its pathogenesis, especially since a preventable cause has been suggested.

Table 8 Cases of haemorrhagic shock encephalopathy syndrome 1982-88

1982	1983	1984	1985	1986	1987	1988
13	22	9	11	7	18	16

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Chemistry set poisoning

The objectives of the survey were to determine the incidence and source of poisoning due to exposure to toxic chemicals intended to be handled by children, and secondly to assess whether packaging, easy access, or other risk factors contributed to the poisoning.

Seventeen cases were reported over 16 months (January 1991 to April 1992), but one was a duplicate and two did not fulfil the definition, leaving 14 for analysis. There were nine boys and five girls aged from 20 months to 15 years, six of them under 3 years of age. Seven episodes were associated with copper sulphate, three cobalt chloride, two methylene blue, and one each to ammonium sulphide and tartaric acid. The source was a chemistry set in eight, crystal growing set in three, microscope set in two, and stink bomb in one. The packaging was considered to be unsatisfactory in all eight for which it was known. The risk factors identified were lack of supervision in eight, emotional factors in four, a genuine accident in one, and unknown in one. Thirteen children made an uneventful recovery, and one died from an irreversible cardiac arrest three hours after drinking only one mouthful of a saturated solution of copper sulphate, despite immediate transfer to hospital.

A subsequent retrospective survey of the National Poisons Centre in the UK and Eire for the same period identified a further 19 new cases of chemistry set poisoning from the six out of eight centres whose data were accessible, giving a combined total of 33 cases from the two surveys. Fourteen cases were due to copper sulphate; four to cobalt chloride; three each to ammonium sulphide, tartaric acid, and methylene blue; three to miscellaneous agents, and three unknown.

The index case[1] in April 1989 evoked considerable publicity in the news nedia about the dangers of chemistry sets. More parents became aware of the danger, and sales declined, and this led to a considerable decrease in poisoning incidents. Crystal growing sets were withdrawn from sale in November 1990. Thus, the prospective survey was undertaken at a time when the incidence was already falling. Some cases may have been missed because they were seen by the 10% of paediatricians who did not respond to the survey, or were dealt with by other groups of doctors – for example, in accident and emergency or intensive care units, or general practitioners.

It was concluded that chemistry set poisoning was a definite problem. The sets contained toxic chemicals, readily available to the public, which sometimes got into inappropriate hands[2], and whose use was often unsupervised. Subsequently, four recommendations about child resistant containers, toxic hazard warnings, and the size and content of the lettering were incorporated into EEC Standard EN71 P4, 1990.

Two additional recommendations were, firstly, that the parents of the most vulnerable groups (infants in the second 6 months, toddlers, and nursery school children) should be targeted in health education programmes; and secondly, that chemicals included in sets should be restricted by law. Copper sulphate and cobalt chloride are restricted in the State of Victoria, Australia, where asbestos, ammonium nitrate, and lithium hydroxide are specifically prohibited (Elaine Ogilvie, personal communication, 1992).

A ban on copper sulphate and cobalt chloride, is included, as well as the first four, in proposals for change to British Standard BS 5665 Part 4, 1990 "Specification for experimental sets for chemistry and related activities" submitted by Chris Armstrong on behalf of the Institute of Trading Standards Administration.

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Insulin dependent diabetes

Two studies of insulin dependent diabetes have been coordinated in Bristol using the framework of the BPASU.

The first study, in 1988, was designed to ascertain the incidence of insulin dependent diabetes diagnosed in children under 15 years in the United Kingdom (UK). This was the first national incidence study since the publication of 1973/74 data from the British Diabetic Association register[1]. The results of our study[2] corroborated those of smaller local studies[3,4,5] in finding a considerably higher incidence (13.5 per 100 000 children under 15 per year compared with 7.7/100 000/year for 1973/74). In addition, a quarter of the children diagnosed in 1988 were under 5 years of age, as compared with only 19% in 1973/74. The incidence was highest in Scotland and lowest in the Republic of Ireland (table 9). A winter peak and possible summer trough was most apparent among older children. Case ascertainment was estimated to be 90%.

Our second study considered the incidence of diabetes in children under 5 years in the UK. The results suggested that the annual incidence in this age group had not changed, being 9.3/100 000 in 1992, and 9.9/100 000 in 1988. Regional rates again varied widely (table 9), but there were no seasonal differences in the onset of diabetes in this group of young children. The ascertainment rate for the study as a whole was estimated to be 99%[6]. In regions where two additional case sources were available as well as the BPASU, the BPASU ascertainment rates were estimated to be 78%.

Both studies were designed to define possible aetiological factors in the pathogenesis of childhood onset diabetes. Postal questionnaires were sent to families of cases. In 1992, families of age and sex matched controls were also surveyed. The results of the 1988 questionnaire[7] suggested that the family characteristics associated with diabetes included heavier birth weight, method of infant feeding, the age at onset of type I diabetes of affected fathers and siblings, and the family lifestyle as defined by the father's social class. Data from the 1992 case and control questionnaires, relating to children under 5 years of age, revealed increased risks of diabetes associated with paternal insulin dependent diabetes, being firstborn, and younger paternal age[8]. They also showed that children who develop diabetes between the ages of 1 and 2 years were more likely to have a parental history of type I diabetes than older children.

The addition of diabetes to the reporting card, most particularly in 1988, undoubtedly increased the workload of paediatricians, but it was important to ascertain the national incidence of diabetes. In addition, the linking the BPASU system to a parental self completion questionnaire (and in 1992 case and control questionnaire) allowed hypotheses about the aetiology of diabetes in childhood to be tested.

Table 9 Regional incidence of insulin dependent diabetes in children under 5 years in 1988 and 1992

Region	1988			1992		
	Cases	Population < 5 years*	Incidence per 100000 population	Cases	Population < 5 years†	Incidence per 100000 population
Scotland	45	322989	13.93	51	326341	15.63
Northern	21	198095	10.60	29	202658	14.31
Mersey	17	160342	10.60	22	165267	13.31
Oxford	19	172804	11.00	23	181619	12.66
East Anglia	20	131456	15.21	14	134471	10.41
West Midlands	28	346605	8.08	38	364312	10.43
Northern Ireland	10	136862	7.31	13	129318	10.05
Wessex	21	181849	11.55	19	190630	9.97
NW Thames	14	231952	6.04	21	245240	8.56
Wales	19	185956	10.22	16	191905	8.34
Yorkshire	26	240037	10.83	21	252271	8.32
SE Thames	18	234325	7.68	20	252720	7.91
South Western	24	195508	12.28	15	206083	7.28
SW Thames	16	182932	8.75	14	195962	7.14
Eire	16	324078	4.94	19	273730	6.94
NE Thames	29	256705	11.30	18	272037	6.62
Trent	27	297275	9.08	18	313616	5.74
North Western	34	271679	12.51	16	285790	5.60
Total	404	4071449	9.92	387	4183970	9.25

* Data from: General Register Office for Scotland, mid-1988 estimates based on 1981 census; OPCS, estimated resident population at mid-1988 based on 1981 census; General Register Office for Northern Ireland, mid-1988 estimates based on 1981 census; Central Statistics Office for the Republic of Ireland, population figures issued in the 1986 census.

† Data from: General Register Office for Scotland, mid-1992 estimates based on 1991 census; OPCS, estimated resident population for 1992 based on the 1991 census; General Register Office for Northern Ireland, mid-1992 estimates based on 1991 census; Central Statistics Office for the Republic of Ireland, population figures issued in the 1991 census.

The databases of both studies are currently being re-examined in a joint venture with the Wellcome Trust Centre for Human Genetics in Oxford to establish a "DNA bank" using filter paper blood spots and buccal smear mouth swabs from the parents and children who took part in the 1988 and 1992 studies. The combination of genetic and epidemiological data has the potential for substantially advancing our understanding of the aetiology of childhood onset insulin dependent diabetes.

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Rett syndrome

Rett syndrome is essentially a developmental disorder, and is responsible for profound motor and learning phenomena, such as developmentally triggered regression, breathing dysrhythmia, and the preservation of charming personality in spite of enormous disabilities.

Research into Rett syndrome began in Glasgow in 1982 and received an important boost in April 1990 when the surveillance unit agreed to circulate information about it. The unit invited paediatricians to report in each of three months and subsequently reminded them that the survey remained open for reports of probable cases, male or female, regardless of age.

Between 1982 and 1 May 1995, 670 reports had been made and new cases were still appearing each week. Sufficient data were available to confirm or exclude the diagnosis in 535 (80%), 451 of whom (84%) had classic Rett syndrome, 52 (10%) were mildly atypical cases, and 33 (6%) did not have Rett syndrome. Six males had been reported, none of whom had classic features.

About 30 cases are reported each year between the ages of 8 and 15 years. The prevalence of classic Rett syndrome throughout childhood and into adult life is thought to be one in 10000 females. The steady flow of new cases indicates that many cases have yet to be reported. The difference in disability found between monozygotic twins suggests that there are more people with Rett disorder than show the classic syndrome.

Twenty-two deaths have occurred within the series (about 1% of known cases each year). The deaths seem not to have been caused by progression of the disorder. Feeding difficulties and poor nutrition have contributed in several but death is often sudden and unexpected. Most women with Rett Syndrome live long and enjoy good health in spite of their dependent state and liability to increasing muscle tone and deformity. One hundred and sixty-three women have been reported over 20 years of age (24% of all reports).

Due to excellent support from physicians, families, the National and UK Rett Syndrome Associations, and Quarriers Homes several hundred families have agreed to complete annual health questionnaires. This unit plans to send them personally until July 1998. These questionnaires are supplying a series of projects with data. Permission from each family and approval of regional ethics committees have been obtained for nutritional, neurophysiological, genetic, biochemical, and neuropathological investigations. The effects of therapeutic interventions are measured by means of health indices.

The good survival in spite of the serious consequences of a very disabling disorder, the preponderance of females, the high proportion of classic cases and consistent neuropathological evidence indicate that we are dealing with a core disease entity.

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Higher order births

The aim of this study was to determine prospectively the number of triplets and higher order births born in one calendar year (1989), and to assess what proportion were spontaneous conceptions and the implications for neonatal intensive care facilities. BPASU respondents were asked to complete a brief questionnaire whenever they had been involved in the management of triplets or higher order births and to send the questionnaires to obstetric and gynaecological colleagues in order to obtain information about the conception and pregnancy[1].

We were notified of 143 sets of triplets, 12 quadruplets, and one of quintuplets, a total of 482 babies. We learnt the method of conception for 153 of the 156 pregnancies, 31% of which were spontaneous. Thirty-four per cent resulted from various methods of ovarian stimulation, 24% of occurred after in vitro fertilisation (IVF), and 11% resulted from gamete in vitro fallopian transfer (GIFT). Mothers who underwent IVF were significantly older than those in whom ovulation was induced.

In almost half of the pregnancies in which reproduction was assisted, ovarian stimulation was used rather than the more sophisticated IVF or GIFT procedures. None of the quadruplet or quintuplet pregnancies occurred spontaneously. The Voluntary Licensing Authority stated that 'no more than three eggs or pre-embryos should be transferred in any one cycle, unless there are exceptional clinical reasons', but in five cases four embryos were inserted. A further concern was that in half of the GIFT pregnancies, more than four eggs were replaced. GIFT was a relatively new technique and not covered by the *Human Fertilisation Act 1990*.

The perinatal mortality rate was 70 per 1000 total births for triplets and 104 per 1000 for quadruplets. The median gestational age at birth was 33 completed weeks for triplets and 31 weeks for quadruplets and quintuplets. The median birth weight was 1700g (range 340 to 3330g). The median length of stay in a neonatal unit was 25 days (range 1 to 171 days). Forty-five per cent of babies required mechanical ventilation for a median duration of four days (range 1 to 104 days). The risk of congenital abnormalities was greatest in naturally conceived pregnancies.

In conclusion, this study supports the observed progressive and very steep rise in the triplet and higher order births in Britain. We showed that assisted reproduction was the commonest cause of triplet and higher multiple births and that ovarian stimulation was the commonest technique in use at that time. These babies are very likely to be born before term and make considerable demand on neonatal intensive care facilities.

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Galactosaemia

The object of the study was to investigate the need for newborn screening for classical galactosaemia (galactose-10-phosphate uridyl transferase deficiency). Screening is already in routine use in the Republic of Ireland and Scotland, but not in other parts of the UK. Cases were reported to the BPASU from January 1988 to September 1991, but data were only analysed for the three complete years 1988 to 1990. Sixty cases were diagnosed, 46 in unscreened and 14 in screened areas (table 10). The incidence of the disease, one in 44 000 in the UK and one in 23 000 in the Republic of Ireland, was higher than expected from previous estimates.

Table 10 Distribution of cases of galactosaemia

Year	Cases (No.)	Unscreened: England/Wales/ N Ireland	Screened: Scotland	Screened: Republic of Ireland
1988	25	17	2	6
1989	19	16	3	0
1990	16	13	2	1

For the following reasons we concluded that the introduction of new screening programmes throughout the UK was not justified[1]:

1. *Screening does not reduce acute illness:* Encephalopathy, coagulopathy, septicaemia, and jaundice requiring exchange transfusion occurred in four out of 14 in the screened group and nine out of 46 in the unscreened group.
2. *No excess of previous sibling deaths attributable to galactosaemia was found in the unscreened group:* One previous sibling death occurred in the unscreened areas and two deaths in the screened areas at the time when the screening programmes were already in place.
3. *Screening may not prevent early death:* One patient died at 4 days in the unscreened group due to coliform septicaemia. Existing programmes screen at 6 to 10 days and would not have prevented this death.
4. *The age of starting dietary treatment is not delayed unduly in the unscreened group*: Two cases were diagnosed after two months in the unscreened group, but with greater clinical vigilance signs of the disease could have been detected much earlier. Treatment was delayed in one case in the screened group who displayed severe neonatal illness.
5. *The existing phenylketonuria screening programme can contribute to early diagnosis of galactosaemia:* Galactosaemia causes moderate increases in phenylalanine and tyrosine[2]. Selective screening of patients with hyperphenylalaninaemia for galactosaemia detected nine out of 60 cases in the study.

The BPASU Study has contributed to two further projects on galactosaemia. A galactosaemia register has been set up in collaboration with the British Paediatric Association Research Unit. The BPASU study provided useful experience on methods of recruiting patients to the register. A follow up of patients from the BPASU cohort are being followed up in their eighth year to determine the cause of long term complications. It has become clear that a high proportion of study patients have been lost to follow up and many others are not being seen in specialist metabolic clinics.

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Congenital toxoplasmosis

Background

Towards the end of 1988 congenital toxoplasmosis was covered extensively in the public and professional media. This was provoked by a publication which suggested that congenital toxoplasmosis made a significant contribution to the burden of severe mental and physical disability in the UK and that the introduction of national prenatal screening should be considered.

The publicity continued into 1989 and public and professional pressure for screening increased. Proponents estimated that about 40 to 70 babies were born with neurological damage apparent at birth or in early infancy in England and Wales each year. These figures were based on data derived from local serological surveys of pregnant women in the UK. The estimates also used rates of transplacental transmission and proportions of babies severely clinically affected at birth obtained from studies conducted in other countries up to two decades earlier.

Mass prenatal screening may cause significant harm (for example, through the loss of uninfected fetuses) and it was important to determine whether this harm could be outweighed by the cases of congenital toxoplasmosis prevented by such a programme. Our survey asked paediatricians to report all cases newly diagnosed by them from June 1989 to 31 May 1990 so that we could determine the number of diagnosed cases belonging to that birth cohort in England and Wales and compare it with the estimated figure. Our secondary objectives were to determine how cases were diagnosed, their degree of impairment and how they were managed.

Methods

Case ascertainment through the BPASU was supplemented (for England and Wales) by routine reports of toxoplasmosis from microbiologists to CDSC.

Further information on reported cases was obtained from reporting paediatricians and microbiologists. A series of clinical and serological criteria were used in the analysis to designate cases as 'definitely', 'probably', 'possibly', or not congenitally infected.

Results

Eighty-six cases were initially reported (40 through BPASU and 52 through CDSC, six of which were common to both), 37 of which were considered definite/probable/possible cases. Nearly half of the remainder were neonates initially considered infected but who lost antibody in the first year of life; others had been diagnosed before the study period or had acquired infection postnatally.

Among the 37 cases of definite or suspected congenital toxoplasmosis, 14 belonged to the study year birth cohort whereas 23 were born before the study started. Fifteen of the 23 were children over 6 years of age with newly diagnosed retinochoroiditis. Taking only those cases who were both symptomatic and born in England and Wales between 1 June 1988 and 31 May 1990 (that is, including subjects from the previous annual birth cohort diagnosed in their second year of life to compensate for loss of such cases from the study year birth cohort) there were a total of 17. In three of the 17, the diagnosis was only "possible", because of non-specific signs and incomplete serological confirmation. Only nine cases had evidence of central nervous system involvement.

Comment

The main finding of this survey was the disparity between the number of observed cases with neurological manifestations in infancy (nine) and the estimated number (40-70). Only five had the 'classic triad' of hydrocephalus, intracranial calcification, and retinochoroiditis. Paediatricians experienced considerable difficulty in diagnosing congenital toxoplasmosis because of its non-specific clinical features and the problems of undertaking long term serological follow up. The management of cases with similar clinical manifestations varied considerably. Older children who presented with retinochoroiditis were often managed by ophthalmologists without paediatric support.

The survey's findings were taken into account by a working party set up by the Royal College of Obstetricians and Gynaecologists to review the pros and cons of setting up a national prenatal screening programme for toxoplasmosis. The working party recommended to the profession and to the Department of Health that such a programme should *not* be introduced in the UK at present because the size of the problem of severe symptomatic congenital toxoplasmosis was likely to be too small to outweigh the harm that the programme might cause.

Because of the disparity between observed and estimated numbers, however, further research was needed. Underdiagnosis and/or underreporting may have contributed, but it is unlikely that sufficient cases severely affected at birth would have gone unrecognised to explain the difference.

Acknowledgment

This survey, like all BPASU surveys, depended entirely on the good will of paediatricians in providing detailed information on reported cases – thank you to the many colleagues involved.

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10 International developments

The strength of the BPASU's methodology is such that it has been adapted successfully in several other countries. Six countries have now developed 'active' surveillance systems to monitor rare disorders, along similar lines to the BPASU. The national units in the Netherlands, Germany, and Switzerland have developed a close liaison with the BPASU and several studies are being conducted simultaneously in the four units using similar research protocols to produce larger pools of data for analysis.

Representatives of the European units met in Leiden in January 1995. Each unit presented a report. Subsequently, discussion centred on developing links between researchers and units and it was agreed that meetings between researchers and between units should be held more often. Several studies are to be undertaken simultaneously, using similar study protocols where possible. Funding is being sought from the Biomed programme.

German Paediatric Surveillance Unit

Encouraged by the success of the BPASU, a German adaptation of the surveillance scheme, called the Erhebungseinheit für Seltene Pädiatrische Erkkrankungen in Deutschland (ESPED) was set up in July 1992. The reporting system differs slightly from that of BPASU, in that cards are sent to heads of departments for completion. Four hundred and eighty clinicians receive reporting cards and the response rate has risen significantly from 75% in 1992 to 93% in 1994. Ninety per cent of the questionnaires sent out by researchers are returned.

Twelve studies have been undertaken. These include *Haemophilus influenzae* type b, Reye's syndrome, insulin dependent diabetes mellitus in children under 5, neonatal thrombosis, Ondine's curse (primary failure of respiratory regulation), Kawasaki disease, acute renal failure, acute liver failure, acute immune hepatitis, and complications of pertussis.

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Netherlands Paediatric Surveillance Unit

The Netherlands unit began surveillance in October 1992. About 350 paediatricians in 152 general hospitals receive the card each month. The eight university hospitals have each nominated specific personnel to respond for separate disorders and to be responsible for reporting all cases in that hospital. The overall response rate has risen from 83% in 1992 to 93% in 1995. The follow up rate is also high at 93%. Participants recognise the importance of full case ascertainment and, where possible, additional respondents are recruited for particular disorders. Surveillance of diabetes was supported by the collaboration with the Dutch Diabetic Association and the Netherlands Reference Laboratory Bacterial Meningitis acted as a secondary source for Hib surveillance.

Eleven studies have been undertaken, three of which have now been completed, These included insulin dependent diabetes mellitus, neural tube defects, Hib, sickle cell disease, coeliac disease, haemorrhagic disease of the newborn, acute flaccid paralysis, AIDS/HIV, haemolytic disease of the newborn (non-ABO non-Rh), thalassaemia major, and postneonatal mortality in children born premature and dysmature.

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Switzerland Paediatric Surveillance Unit (SPSU)

The SPSU was set up early in 1995 under the auspices of the Swiss Paediatric Association and the Federal Office of Public Health. Reporting cards are being circulated to 500 respondents in 41 clinics and the response rate so far is 98%. Four studies are being undertaken: vitamin K deficiency bleeding, acute flaccid paralysis, congenital rubella, and toxoplasmosis. The German unit has provided software to run the system and is currently advising the SPSU.

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Australian Paediatric Surveillance Unit (APSU)

The APSU became active in May 1993, and it currently circulates reporting cards to 930 clinicians, with an average response rate of 90%. The response rate for general paediatricians was 91%, and for paediatric subspecialties the response rate varied from 79% to 100% with a mean of 90%. Rates were lower for some non-paediatric specialists. In 1994, 69% of clinicians had nothing to report, 25%

reported one case, 5% reported two to four cases, and less than 1% reported more than five cases.

Twelve conditions, including a number of infectious and vaccine preventable diseases, are currently being surveyed. These include congenital rubella, drowning and near drowning, extrahepatic biliary atresia, haemorrhagic disease of the newborn, HIV/AIDS, haemolytic uraemic syndrome, subacute sclerosing panencephalitis, acute flaccid paralysis, congenital and neonatal varicella, severe combined immunodeficiency, and congenital adrenal hyperplasia. Studies of childhood dementia, Kawasaki disease, and Rett syndrome have been completed.

The APSU has provided data to the National Health and Medical Research Council of Australia, the World Health Organisation, the International Committee for Vitamin K Deficiency Surveillance, and the Commonwealth and State Health Departments. It has received considerable attention from the national media and the medical press, through which it has informed both the general public and the wider medical community of its activities. Negotiations between the APSU and the New Zealand Paediatric Society continue with the aim of including New Zealand paediatricians on the mailing list.

The APSU has recently published its second annual report and this is available on request.

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Malaysian Paediatric Surveillance Unit (MPSU)

The MPSU was set up in December 1993 and surveillance began in September 1994 under the auspices of the Malaysian Paediatric Association. All 14 regions of Malaysia are included, covering a total population of 19 million, 7 million of whom are children. There are about 600 000 births each year, a total similar to that in the UK. The unit adopts the same methodology as the BPASU. Reporting cards are circulated to 239 paediatricians and surgeons. The initial response rate is encouraging at 70%, and this figure is expected to rise as the system becomes more familiar. Only 13% of respondents have never returned a card. Initially three conditions are under surveillance, paediatric HIV and AIDS, acute fulminant liver failure, and death from asthma.

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Several other countries are considering developing surveillance systems on the lines of the BPASU. These include Canada, New Zealand, Turkey, Hungary, and Papua New Guinea.

11 BPASU scientific seminar

To herald the unit's tenth year of surveillance a one day scientific seminar was held in June 1995 at the PHLS Central Public Health Laboratory in Colindale, North London. The aim of the seminar was to review the BPASU's contribution to national surveillance, understanding and control of rare conditions in childhood, and to identify future applications of the BPASU mechanism. Over a hundred paediatricians, researchers, and epidemiologists attended the meeting, along with representatives from our sister paediatric surveillance units in the Netherlands, Germany, and Malaysia, and from the British Neurology Surveillance Unit.

The morning session concentrated on studies that had provided particularly valuable lessons for the operation of the unit. Dr Elizabeth Miller (PHLS) highlighted the importance of a clinical reporting scheme for surveillance of rare vaccine preventable and vaccine associated conditions, using congenital rubella, SSPE, and meningoencephalitis after MMR vaccine as examples. For such disorders, ascertainment needs to be as complete as possible, for which BPASU reporting must be complemented by other reporting systems. The importance of this point was highlighted in the study of meningoencephalitis after MMR, in which relatively few cases were picked up by the BPASU. Many of the final total were identified by microbiologists. Dr Miller raised concern about the removal of SSPE from the orange card. It had been hoped that cases would be reported through other routes but these may not be sufficiently reliable, so the BPASU has agreed to reinstate SSPE.

Dr Paul Heath of the Oxford Haemophilus Reference Laboratory presented data from the Hib vaccine efficacy study. He said that 36% of suspected vaccine failure cases reported to date had not been ascertained through the BPASU but through microbiologists and public health physicians. He emphasised the value of telephone reporting in ensuring that specimens were collected for rapid confirmation of cases. It was stated, however, that some telephone reports had not been followed by an orange card report, which caused problems for the BPASU's administrative and self monitoring system.

Methodological aspects of two relatively common disorders, congenital dislocation of the hip and diabetes in under 5s, ascertained through the BPASU were presented by Dr Carol Dezateux and Dr Julian Shield. Both studies highlighted the value of using more than one data source to maximise case ascertainment. Other problems included matching data between sources, respondents remembering whether cases had been reported, and the substantial workload of such studies. Concerns were also expressed that the demise of regional health authorities might lead to increasing problems with using Hospital Episode Statistics for validation of the completeness of ascertainment.

In the afternoon session, Dr Ruth Gilbert gave an overview of lessons learnt by the unit, which included a description of complementary data sources. Dr Tony Ades (ICH, London) spoke about capture-recapture methods as a means of estimating the 'true' size of a population. Professor Brent Taylor (Royal Free Hospital) then took us into the 'electronic future' using the Child Health Information System as an example. A presentation on ethics and confidentiality opened a detailed discussion over the ethics of collecting and holding data for epidemiological studies. Approval is more difficult to obtain for research than audit and surveillance appears to be a 'grey area'. All agreed on the need for a national ethics committee to approve national studies. Finally, Dr John Tripp (Royal Devon and Exeter Hospital) discussed links with other European surveillance systems. Using vitamin K deficiency bleeding as an example, the problem of agreeing case definitions, and study protocol, and allowing for differences in the populations and differences in management were discussed.

It is hoped that a summary of the proceedings of the meeting will be published, but if anyone would like the abstracts of the meeting please contact the BPASU office.

12 Completed studies

The BPASU has now completed 21 studies. Information about these studies has been included in previous annual reports of the surveillance unit, which are available from the BPASU office. The studies and their principal investigators are listed below. For addresses see the list at the end of this report.

1. **X-linked anhydrotic ectodermal dysplasia**
   (June 1986 – August 1986)
   Dr A Clarke
2. **Lowe syndrome**
   (June 1986 – February 1988)
   Dr C McKeown
3. **Insulin dependent diabetes in under 15s**
   (January 1988 – December 1988)
   Professor J D Baum
4. **Drowning and near drowning**
   (January 1988 – December 1989)
   Professor J Sibert
5. **Higher order births**
   (January 1989 – December 1989)
   Professor M Levene
6. **Haemorrhagic disease of the newborn**
   (March 1988 – February 1990)
   Dr A W McNinch, Dr H Tripp
7. **Haemorrhagic shock encephalopathy syndrome**
   (June 1986 – December 1988)
   Dr S Hall
8. **Haemolytic uraemic syndrome**
   (June 1986 – December 1989)
   Dr S Hall
9. **Kawasaki disease**
   (June 1986 – December 1992)
   Dr S Hall
10. **Congenital toxoplasmosis**
    (June 1989 – May 1990)
    Dr S Hall
11. **Acute rheumatic fever**
    (January 1990 – December 1990)
    Dr C Boyd-Scobie, Dr S Hall
12. **Rett syndrome**
    (April 1990 – June 1990)
    Dr A Kerr
13. **Measles, mumps, rubella/meningococcal meningitis**
    (January 1990 – December 1991)
    Dr N Begg
14. **Neonatal herpes**
    (June 1986 – Dec 1991)
    Ms P A Tookey, Professor C S Peckham, Dr R Dinwiddie
15. **Chemistry set poisoning**
    (January 1991 – April 1992)
    Dr E Mucklow
16. **Galactosaemia**
    (January 1988 – September 1991)
    Mrs A Green, Dr J Holton, Dr M Honeyman, Professor J Leonard
17. **Long term parenteral nutrition**
    (February 1992 – April 1992)
    Professor D Candy, Professor E Ross, Dr S Devane
18. **Insulin dependent diabetes**
    (January 1992 – December 1992)
    Professor J D Baum, Ms E Wadsworth
19. **Androgen insensitivity syndrome**
    (September 1991 – August 1993)
    Professor I A Hughes
20. **Juvenile dermatomyositis**
    (June 1992 – December 1993)
    Dr D Symmons, Dr A Sills
21. **Congenital dislocation of the hip**
    (April 1993 – July 1993)
    Dr C Dezateux, Ms S Godward

13 Publications 1994–1995

Published papers

Miller E, Tookey P, Morgan-Capner P, Hesketh L, Brown D, Waight P, et al. Rubella surveillance to June 1994: third joint report from the PHLS and the National Congenital Rubella Surveillance Programme. *Communicable Disease Report* 1994; 4: R146–52.

Kemp AM, Mott AM, Sibert JR. Accidents and child abuse in bathtub submersions. *Arch Dis Child* 1994; **70**: 435–8.

Hirst WJ, Layton DM, Singh S, Mieli-Vergan G, Chessells, JM, Pritchard J, et al. Haemophagocytic lymphohistiocytosis: experience at two UK centres. *Br J Haematol* 1994; **88**: 731–9.

Wagner R, Morgan G, Strobel S. A prospective study of CD45 isoform expression in haemophagocytic lymphohistiocytosis; an abnormal inherited immunophenotype in one family. *Clin Exp Immunol* 1995; **99**: 216–20.

Gibb DM, Davison CF, Holland FJ, Walters S, Novelli V, Mok J. Pneumocystis carinii pneumonia in vertically acquired HIV infection in the UK. *Arch Dis Child* 1994; **70**: 241–4.

Dunn DT, Nicoll A, Holland FJ, Davison CF. How much paediatric HIV infection could be prevented by antenatal HIV testing? *J Med Screen* 1995; **2**: 35–40.

Gibb DM, Fauknell W, Nokes I, Appleby S, Holland FJ, Berry T, et al. Coverage of routine neonatal metabolic screening in children born to women known to be infected with HIV-1. *Communicable Disease Report* 1995; **5**: R123–4.

Abstracts and conferences proceedings

Nicoll A, Ades AE, McGarrigle C, Weerasuriya M, Kennedy R, Goldberg D. The epidemiology of HIV-1 infection in pregnant women in the United Kingdom. *Poster presentation at Medical Research Council meeting, Manchester, September 1994.*

European Society for Paediatric Research 1995 Annual Meeting 1995:

Tookey P. Surveillance of congenital rubella in England, Scotland, and Wales.

Wadsworth EJK, Shield JPH, Hirasing RA, Herzig P, Rosenbauer J, et al. Diabetes incidence and ascertainment in children under 5 years for the UK, the Netherlands, and Germany.

Conyn-van-Spaendonck MAE, Heath P, Slack M, von Kries R. Paediatric Surveillance as a tool for the evaluation of National Immunisation Programmes, particularly of immunisation against invasive infections by Haemophilus influenzae type b.

Cornelissen M, McNinch A, Tripp J, Shrubiger G, Loughnan, von Kries R. Prospective studies on vitamin K deficiency bleeding in various countries.

Abstracts published in *Paediatric Research* 1995: **38**: 423–33.

14 Presentations of BPASU studies 1994–1995

BPA Annual Scientific Meeting 1994

Morbidity due to non-PCP respiratory disease in paediatric HIV infection. Sharland M, Davison C, Davies E, Walters S, Gibb D.

Neonatal herpes surveillance 1986-1991. Tookey PA.

Androgen insensitivity syndrome; diagnostic yield in the complete and partial forms. Teoh Y, Patterson MN, Hughes AI.

Estimation of BPASU study ascertainment rate using a statistical capture-recapture technique. Wadsworth E, Shield JPH, Lynn R, Baum JD.

BPA Annual Scientific Meeting 1995

Invasive Haemophilus influenzae infection following Hib immunisation. Heath P, Booy R, Slack M, Begg N, Griffiths H, Anderson E, Bird G, Chapel H, Moxon R.

Paternal uniparental isodisomy of chromosome 6 is a cause of transient neonatal diabetes. Temple IK, Shield JPH, James RS, Crolla JA, Sitch FL, Betts P, Howell W, Baum JD, Jacobs PA.

Epidemiology of Munchausen syndrome by proxy, non-accidental poisoning and suffocation. McClure RJ, Davis P, Sibert JR, Meadow SR.

Screening for congenitally dislocated hips reappraised. Dezateux C.

Incidence of juvenile dermatomyositis: results of BPASU survey. Symmons DPM, Sills JA, Davis SM.

Some reflections on vitamin K prophylaxis. McNinch A.

15 Support groups for rare childhood disorders

Congenital dislocation of the hip: STEPS, 15 Statham Close, Lymm, Cheshire WA12 9NN.

Congenital rubella: National Rubella Council, 33–39 Pancras Road, London NW1 2QB.

SENSE (Deaf/Blind Rubella Handicaps), 31 Gray's Inn Road, London WC1X 8PT.

Dermatomyositis and Polymyositis: Dermatomyositis and Polymyositis Support Group, 146 Newtown Road, Woolston, Southampton, Hampshire S02 9HR.

Encephalitis effects: Encephalitis Support Group, 59 Corporation Road, Darlington, County Durham DL3 6AD.

Galactosaemia: Galactosaemia Support Group, Mrs S Bevington 18 Nuthurst, off Reddicap Heath Rd, Sutton Coldfield, W Midlands B75.

Guillain-Barré syndrome: Guillain-Barré Syndrome Support Group, 'Foxley', Holdingham, Sleaford, Lincolnshire NG34 8NR.

Kawasaki disease: Mrs S Davidson, 13 Norwood Grove, Potters Green, Coventry CV2 22FR.

Liver disease: Children's Liver Disease Foundation, 40-42 Stoke Road, Guildford, Surrey GU1 4HS.

Lowe syndrome: Lowe Syndrome Association, 29 Gleneagles Drive, Penworthan, Preston, Lancashire, PR1 0JT.

Meningitis: National Meningitis Trust, Fern House, Bath Road, Stroud, Gloucestershire.

Neonatal herpes: Herpes Association, 41 North Road, London N7 9DP.

Poliomyelitis: Mr L Jackson, British Polio Fellowship, Bell Close, West End Road, Ruislip, Middlesex HA4 6LP.

Rett syndrome: The Rett Syndrome Support Group, Mrs Y Milne, Heartpool, Golden Valley, Castlemorton, Malvern, Worcestershire WR13 6AA.

Reye's syndrome: Reye's Syndrome Foundation of the UK, Mrs G Denney, 15 Nicholas Gardens, Pyrford, Woking, Surrey GU22 8SD.

Haemophagocytic lymphohistiocytosis: Mr C Mallard, Histiocyte Support Group UK, Churchland, 18b City Way, Rochester, Kent ME12AP.

Marcus Nunn Histiocyte Association, Sheep House Road, Bennetts End, Hemel Hempstead HP3 9LW.

For information on various rare childhood disorders a directory of support groups and their addresses has been produced by **'Contact a Family'**, 170 Tottenham Court Road, London W1P OHA.

16 Contact addresses

Ms R Abbott, Infant and Child Nutrition Group, MRC Dunn Nutrition Unit, Downham's Lane, Cambridge CB4 1XJ.

Dr A E Ades, Department of Epidemiology, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Arthritis and Rheumatism Council, Copeman House, St Mary's Court. St Mary's Gate, Chesterfield, Derbyshire S41 7TD.

Dr A Baker, King's College Hospital, Denmark Hill, London SE5 8RX.

Dr C L R Bartlett, PHLS, Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ.

Professor J D Baum, Institute of Child Health, Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ.

Dr N Begg, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ.

Dr R Booy, St Mary's Hospital, Praed Street, London W2 1NY.

British Paediatric Association, 5 St Andrew's Place, Regent's Park, London NW1 4LB.

Professor D Candy, Department of Child Health and Community Paediatrics, King's College School of Medicine and Dentistry, London SWE5 9PJ.

Dr M Catchpole, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ.

Dr A Clarke, University of Wales, Heath Park, Cardiff CF4 4XW.

Dr R R Counahan (BPASU Irish Representative), Paediatric Department, Regional Hospital, Waterford, Republic of Ireland.

Dr P Davis, Department of Community Child Health, Lansdowne Hospital, Sanatorium Road, Cardiff CF1 8UL.

Dr S Devane, Department of Child Health and Community Paediatrics, King's College School of Medicine and Dentistry, London SE5.

Dr C Dezateux, Department of Epidemiology, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Dr R Dhillon, Department of Cardiology, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

Dr R Dinwiddie, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Dr E Elliot, Australian Paediatric Surveillance Unit, PO Box 3315, Parramatta, NSW 2124 Australia.

Faculty of Paediatrics of the Royal College of Physicians of Ireland, 6 Kildare Street, Dublin 2, Republic of Ireland.

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Dr R Gilbert, Department of Epidemiology & Biostatistics, Institute of Child Health, Guilford Street, London WC1N 1EH.

Dr D Goldberg, Scottish Centre for Infection and Environmental Health, Ruchill Hospital, Glasgow G20 9NB.

Mrs A Green, The Child and Family Centre, 142 Maas Road, Northfield, Birmingham B31 2PR.

Dr S Hall, Children's Hospital, Western Bank, Sheffield S10 2TH.

Dr M Guy, Brent and Harrow Health Authority, Harovian Business Village, Bessoborough Road, Harrow HA1 3EX.

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Dr A Kerr, Quarrier's Homes, Bridge of Weir, Renfrewshire PA1 3SA.

Dr M Layton, Department of Haematological Medicine, King's College Hospital, Denmark Hill, London SE5 8RX.

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Professor M Levene, Leeds General Infirmary, Belmont Grove, Leeds LS2 9NS.

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