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An outbreak of erythema infectiosum associated with human parvovirus infection

By M. J. ANDERSON*, E. LEWIS**, I. M. KIDD, S. M. HALL** and B. J. COHEN†

Department of Medical Microbiology, King's College School of Medicine and Dentistry, Denmark Hill, London SE5 8RX
** *Public Health Laboratory Service, Communicable Disease Surveillance Centre, Colindale Avenue, London NW9 5EQ*
† *Public Health Laboratory Service, Virus Reference Laboratory, Colindale Avenue, London NW9 5HT*

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SUMMARY

Erythema infectiosum (EI) or fifth disease is a mild, acute exanthematous disease, occurring mainly among children, for which a causative virus has long been sought. In May 1983 an outbreak of exanthematous illness was reported in a primary school in North London. Children attending the school were investigated by questionnaire and 162 (43·9%) reported an illness with the features of EI. In each of 36 cases investigated virologically the illness was associated with parvovirus infection. Moreoever, pre-existing antibody to parvovirus was correlated with protection from EI in 16 of 17 close family contacts of cases. We propose therefore that EI is the common manifestation of infection with the human parvovirus.

INTRODUCTION

The human parvovirus (Cossart *et al.* 1975; Summers, Jones & Anderson, 1983) has been shown to be the cause of aplastic episodes in sickle cell anaemia (Pattison *et al.* 1981; Serjeant *et al.* 1981) and other chronic haemolytic anaemias (Duncan *et al.* 1983; Kelleher *et al.* 1983; Rao *et al.* 1983). These are rare conditions in the UK, but infection with the virus is common in that 60% of the adult population in the UK are seropositive (Cohen, Mortimer & Pereira, 1983), infection occurring most often in children of primary school age (Edwards *et al.* 1981). The symptoms which accompany infection in haematologically normal people have until now been obscure. Nine of the original 11 infected individuals were asymptomatic, but subsequently sporadic cases of infection associated with febrile illness have been reported (Paver & Clarke, 1976; Shneerson, Mortimer & Vandervelde, 1980). In addition there have been two cases of erythematous rash in association with parvovirus infection (Paver & Clarke, 1976; Cant & Widdows, 1975) and the possibility that the common clinical manifestation of infection with the human

* Present address and address for correspondence: Department of Medical Microbiology, Faculty of Clinical Sciences, University College London, University Street, London WC1E 6JJ.

parvovirus might be a febrile illness with erythematous rash thus seemed worthy of investigation.

Fifth disease or erythema infectiosum (EI) has been recognized as a separate clinical entity since 1926 (Herrick, 1926), having previously been regarded as an atypical form of rubella (Ischamer, 1889). Classically it begins with erythema of the cheeks giving the so-called 'slapped cheek' appearance. The rash progresses to the trunk and limbs and is maculopapular, often with a reticular or lacy appearance. The rash usually fades within a week but transient recrudescences may occur. Constitutional symptoms are few.

EI has always been assumed to be due to a virus (Balfour, 1976; Gershon, 1979) although the causative agent has proved elusive; in 1972 Balfour reported isolating rubella virus from 10% and echovirus type 12 from a further 4% of cases in one outbreak (Balfour *et al.* 1972), but later work (Lauer, MaCormack & Wilfert, 1976; Cramp & Armstrong, 1976) showed that neither of these viruses was the principal cause of this disease.

In May 1983, following the clinical diagnosis of a case of scarlet fever in a north London primary school, the advice of the Communicable Disease Surveillance Centre (CDSC) was sought regarding possible closure of the school. Enquiry revealed that there had been a number of similar cases of illness with rash in the school in the preceding two months. Clinically the outbreak appeared to be one of EI. This afforded us the opportunity of documenting the cases and investigating the human parvovirus as a possible causative agent of EI.

METHODS

Case study

Enquiry indicated that the outbreak of erythematous rashes had begun in the school during the last week of February 1983. Accordingly a questionnaire was sent during May to the parents of each of the 430 children in the school, inquiring about any illness with a rash among the children and their families occurring since that time. The questionnaire requested details of the clinical features observed by parents, GP consultation, diagnosis and treatment. Children were regarded as cases for inclusion in this study on receipt of a questionnaire documenting an illness accompanied by a rash occurring during the study period.

Virological studies

Cases. In late May and early June, following the informed consent of their parents, finger-prick blood samples were obtained from 30 children who had been involved in the outbreak. These specimens were collected into capillary tubes and the separated serum stored diluted 10^{-2} in assay diluent at -20 °C. Subsequently blood samples were obtained from each member of the eight families of 15 of these children.

Controls. Plasma samples from 22 children aged 1–12 years, resident in southeast London, with no recent history of illness, were kindly supplied by Dr G. Mieli Vergani. Ten heterosexual couples of a similar age to the parents of children at the school, and who had no recent history of illness, constituted the adult control group.

Table 1. *Clinical features of* 162 *children involved in the outbreak*

Rash	Number (%)*	Associated symptoms	Number (%)
Type			
Red cheeks	132 (85)		
Recrudescent	107 (67)		
'Lacy'	93 (60)	Sore throat	51 (32)
Itchy	88 (46)	Headache	46 (28)
		Fever	44 (27)
		Cold/cough	31 (19)
Distribution		Anorexia	30 (18)
Cheeks	141 (87)	Sore eyes	23 (14)
Arms	127 (78)	Arthralgia	12 (7)
Legs	125 (77)	Diarrhoea	12 (7)
Chest	95 (59)	Vomiting	11 (7)
Abdomen/back	82 (51)		
Neck	65 (40)		

* Calculated as the percentage of those completing each section of the questionnaire.

Virus studies

The serum sample from each case was examined for parvovirus DNA by a hybridization spot test (Mason *et al.* 1982) using a cloned portion of human parvovirus genome labelled with ^{32}P (Minson & Anderson, manuscript in preparation). These samples were also examined for parvovirus antigen and parvovirus-specific IgM and IgG class antibodies by radioimmunoassays previously described (Cohen, Mortimer & Pereira, 1983), except that the sera obtained by finger prick were tested at a serum dilution of 10^{-2}. Rubella-specific IgM tests (Mortimer *et al.* 1981) were performed on these sera, using ^{125}I-labelled monoclonal anti-rubella antibody (Tedder, Yao & Anderson, 1982).

Samples from the control groups of children and adults were tested only for parvovirus-specific IgM and IgG antibodies.

RESULTS

Case studies

Questionnaires collected documented 369 children (response rate 86 %) of whom 162 had suffered an illness with erythematous rash. Approximately equal numbers of boys and girls were affected, and the clinical features are shown in Table 1. One hundred and six of the affected children had seen their family doctors. Some parents did not record a diagnosis on the questionnaire, but those reported were: rubella (32), unspecified viral infection (32), allergy (26) and scarlatina/scarlet fever (7). Following initiation of this study and liaison with the general practitioners in the area 18 children were diagnosed clinically as cases of EI.

Figure 1 shows the number of new cases reported per day during the outbreak. The first case occurred on 28 February and no new case was noted after 4 June. Seventy-five per cent of cases occurred during the six-week period of April and the first half of May. Study of the age-specific clinical attack rates among the schoolchildren revealed that EI was most common among the 7- to 10-year-olds (Table 2).

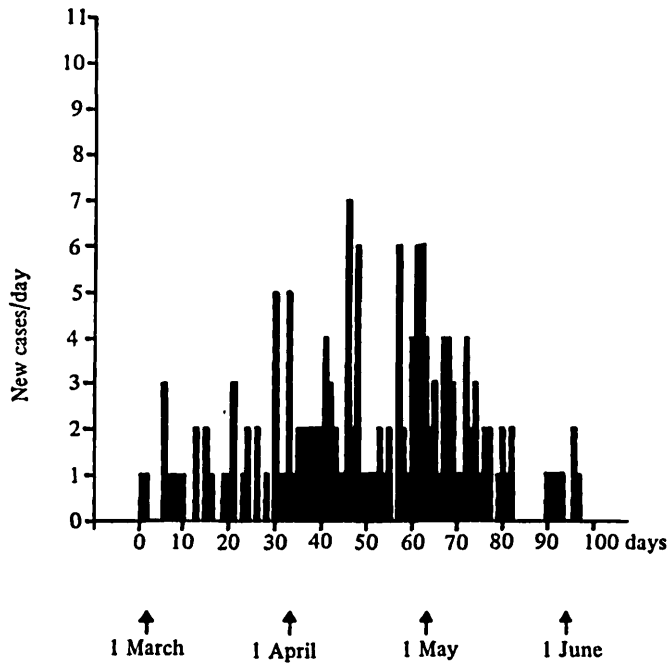

Fig. 1. Distribution of 162 cases of erythema infectiosum by date of onset of rash.

Table 2. *Age-specific clinical attack rates*

Age (years)	Number of children	Number of cases	% Clinical attack rate
4	9	4	44
5	44	16	36
6	47	18	38
7	47	22	47
8	45	24	53
9	61	30	49
10	63	33	62
11	48	12	25

Parents of 149 schoolchildren gave information concerning their households. In 40 families with a child who suffered EI, a similar illness had circulated within the household affecting one or more members not attending the school. As a consequence 53 further cases were identified; 33 of these cases were siblings of the schoolchildren and there were 20 adults. Sixteen of the adults described their symptoms, and gave a clinical picture similar to that reported in the cases among schoolchildren except that arthralgia was noted in 13 (81 %) of adult cases.

Specimens for virus studies could be obtained from only 30 of the schoolchildren involved in the outbreak and from the members of eight families. These eight families comprised a total of 23 members in contact with EI. Six further cases of EI were reported in these contacts, three in adults and three in siblings of an affected pupil. The frequency of reporting of the clinical features characteristic of EI was compared between children identified clinically as cases and those studied

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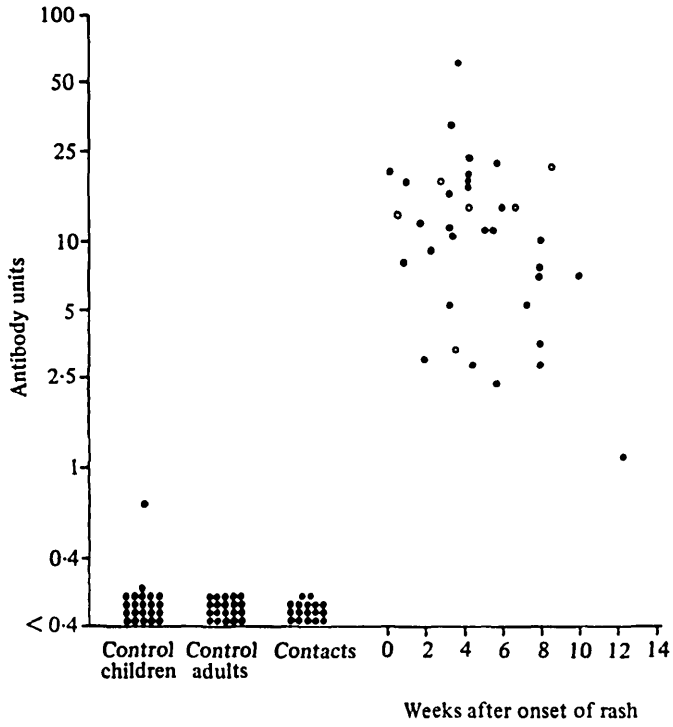

Fig. 2. Parvovirus-specific IgM antibody in controls, asymptomatic contacts, and cases of erythema infectiosum. o, Sera in which trace amounts of rubella-specific IgM antibody were also detected.

virologically; no significant difference was apparent between the groups in the proportions having a 'slapped cheek' appearance or recrudescence of the rash. However, in 80·8% of the children studied virologically, significantly more ($0{\cdot}001 < P < 0{\cdot}01$) than in the clinically identified group (61·5%), the classical, lacy type of rash was reported.

Virological studies

Neither parvovirus DNA nor antigen was detectable in the serum specimens from any of the 36 cases of EI.

Fig. 2. shows the parvovirus-specific IgM titres of the sera from the 36 cases of EI. Each of these specimens contains significant (> 1 unit) amounts of parvovirus-specific IgM antibody. There is an overall trend for the titre of antibody to decline with increasing time following the onset of the rash. In contrast, none of the specimens obtained from the family contacts who remained well gave any reaction in the test. The specimens from the control groups were similarly unreactive, none of the adult control group and only one of the 22 specimens from the control group of children giving any reaction in the test (Fig. 2). This specimen reacted only weakly and did not contain a significant amount of parvovirus-specific IgM (i.e. < 1 unit).

Each of the 33 specimens from childhood cases and the three specimens from adult cases were found to contain high-titre parvovirus-specific IgG (Fig. 3).

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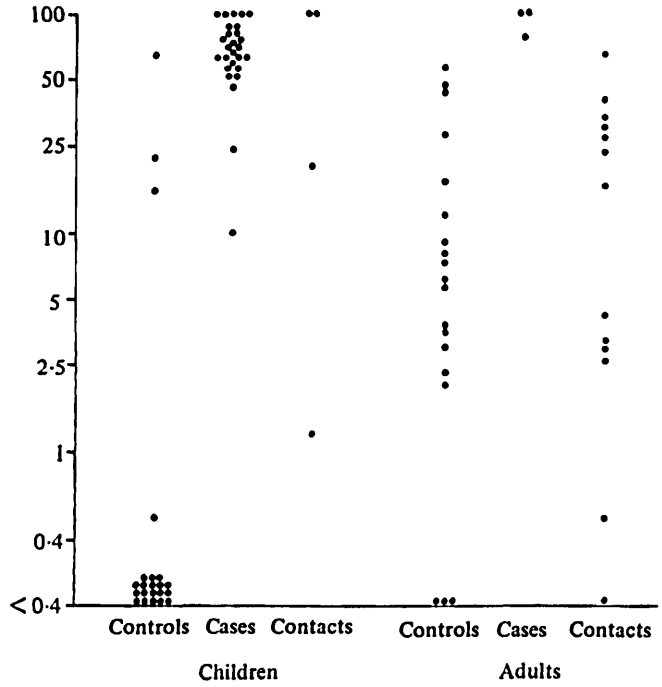

Fig. 3. Parvovirus-specific IgG antibody in controls, cases of erythema infectiosum and asymptomatic contacts.

Specimens from all four sibling contacts and 12 of the 13 adult contacts who had remained well contained detectable parvovirus-specific IgG.

The 36 sera from cases of EI were examined for rubella-specific IgM; 30 were negative while six (Fig. 2) reacted weakly in the test, giving equivocal results ranging from 1·2 to 3·1 arbitrary units.

DISCUSSION

The clinical disease observed in the present study is typical of EI as previously described (Ischamer, 1889; Herrick, 1926; Watts, 1954; Ager, Chin & Poland, 1966; Wadlington & Riley, 1968; Balfour *et al.* 1972; Greenwald & Bashe, 1974; Balfour, 1976; Lauer, MaCormack & Wilfert, 1976; Cramp & Armstrong, 1976; Gershon, 1979). Moreover, the timing of the outbreak described here and the shape of the epidemic curve are remarkably similar to those of the largest published epidemic of EI (Ager *et al.* 1966). This form of epidemic curve is characteristic of person-to-person spread of infection, but in the absence of virus isolation from affected persons and/or transmission studies, the route of infection remains uncertain. It is, however, of interest to note that, in the present study, upper respiratory tract involvement provided the most commonly reported associated symptom.

It is not possible to estimate case-to-case intervals in the epidemic as a whole, although three waves of cases were apparent with an interval of some 15 days. Within the eight families studied two clusters of new cases occurred with intervals of 5–8 days and 11–16 days, both of which accord with previous reports (Ager *et al.* 1966; Wadlington & Riley, 1968; Greenwald & Bashe, 1974).

EI has long been regarded as a transmissible disease (probably viral), due to the epidemic form of outbreaks which are often centred on primary schools, and the increased clinical attack rates observed among family contacts of affected children. Many studies have sought evidence for association of EI with infectious agents (Ager *et al.* 1966; Wadlington & Riley, 1968; Balfour *et al.* 1972; Lauer *et al.* 1976; Cramp & Armstrong, 1976), but no conclusive evidence has hitherto been provided for a causal role for any of these . This is the first outbreak of EI to be examined for evidence of involvement of the human parvovirus.

None of the 42 control sera examined contained significant amounts of parvovirus-specific Igm antibody. This is in accord with previous studies (Anderson *et al.* 1982; Cohen, Mortimer & Pereira, 1983) which have found this antibody to be uncommon, its presence correlating with a history of parvovirus infection occurring during the preceding two to three months. In contrast, all of the serum specimens from the 33 cases of EI contained parvovirus-specific IgM in amounts which declined with increasing time after the onset of the rash. The specimen containing least parvovirus-specific IgM was obtained three months after the onset of the rash. These data suggest that parvovirus infection had occurred at the time of illness in these subjects. Prior to the outbreak of EI these individuals would have had no parvovirus-specific IgG; 82 % of the children and 25 % of the adults would have been susceptible to parvovirus infection. These figures are comparable with the figures of 82 % and 15 % in the control groups of children and adults found to be susceptible to infection. Pre-existing antibody to parvovius was correlated with protection against EI; 16 of 17 family members who had remained well in spite of being in close contact with one or more persons suffering EI were found to have anti-parvovirus IgG antibody, but no detectable parvovirus-specific IgM, indicating past infection with this virus. These data are consistent with parvovirus infection being the cause of EI in this outbreak.

Neither parvovirus antigen nor DNA could be detected in any of the sera from cases of EI. This may be explained by the fact that only four of these specimens were obtained within seven days of the onset of illness. It is likely that EI is a relatively late event in infection; the properties of the rash are consistent with a requirement for a developed immune response in the pathogenesis in a similar fashion to the exanthems of measles and rubella. Within one week of the onset of the rash in rubella, virus can be isolated from the throat in approximately one-half of cases (Haire & Hadden, 1972) while detection of viraemia may be successful in only one tenth of these (Heggie, 1978). It may be therefore that examination of stool or throat specimens would prove more fruitful for virus detection.

There is no doubt that some cases of EI may present a clinical picture identical to rubella, and in Balfour's study (Balfour *et al.* 1972) 10 % of cases of EI had evidence of rubella infection at or near the time of EI. Therefore we tested all sera from cases of EI for rubella-specific IgM antibody. In six (18 %) of the 36 cases, trace amounts of this antibody were present, compatible with rubella infection 2–4 months previously. These six children had suffered EI 4–60 days prior to the specimen being taken, thus the serological data are not consistent with their EI episodes having been caused by rubella. It is of interest to note that the mother of three of these children had recorded on their questionnaires a separate episode of 'German measles with all the classic symptoms – nothing like the slapped cheek rash that appeared later', while a fourth child had been diagnosed by his general

practitioner as suffering rubella some weeks before the onset of EI. Interestingly, at the end of the study reported here a second school notified a number of children with rash illness. In only one of 11 cases studied virologically was this associated with parvovirus infection; the other 10 cases were due to rubella virus.

Previously the human parvovirus has been shown to cause aplastic crises in patients with chronic haemolytic anaemia. To our knowledge such cases are not associated with a rash. In the absence of virus isolates from cases of EI it has not been possible to compare parvovirus from EI cases with that from cases of aplastic crises. None of the children attending the school was known to have a chronic haemolytic anaemia, but cases of aplastic crisis associated with parvovirus infection were noted in a neighbouring area of London shortly after the outbreak of EI described here (Evans *et al.* 1984).

Detailed haematological studies are planned for the future investigation of EI epidemics and it is hoped that this, together with antigenic and genomic analysis of any virus recovered from EI cases, may elucidate the relationship between the causative agent of the two diseases. For the time being we propose that EI is the common manifestation of infection with the human parvovirus and that an aplastic crisis is a clinial manifestation confined to those with a chronic haemolytic anaemia.

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REFERENCES

AGER, E. A., CHIN, T. D. Y. & POLAND, J. D. (1966). Epidemic erythema infectiosum. *New England Journal of Medicine* **275**, 1326–1331.

ANDERSON, M. J., DAVIS, L. R., JONES, S. E., PATTISON, J. R. & SERJEANT, G. R. (1982). The development and use of an antibody capture radioimmunoassay for specific IgM to a human parvovirus-like agent. *Journal of Hygiene* **88**, 309–324.

BALFOUR, H. H. (1976). Fifth disease: full fathom five. *American Journal of Diseases of Children* **130**, 239–240.

BALFOUR, H. H., MAY, D. B., ROTTE, T. C., PHELPS, W. R. & SCHIFT, G. M. (1972). A study of erythema infectiosum: recovery of rubella virus and echovirus 12. *Paediatrics* **50**, 285–290.

CANT, B. & WIDDOWS, T. (1975). Abstract from Conference of the International Society of Blood Transfusion, p. 73.

COHEN, B. J., MORTIMER, P. P. & PEREIRA, M. S. (1983). Diagnostic assays with monoclonal antibodies for the human serum parvovirus-like virus (SPLV). *Journal of Hygiene* **91**, 113–130.

COSSART, Y. E., FIELD, A. M., CANT, B. & WIDDOWS, D. (1975). Parvovirus-like particles in human sera. *Lancet* i, 72–73.

CRAMP, H. E. & ARMSTRONG, B. D. J. (1976). Erythema infectiosum: an outbreak of 'slapped cheek' disease in North Devon. *British Medical Journal* i, 885–886.

DUNCAN, J. R., CAPPELLINI, M. D., ANDERSON, M. J., POTTER, C. G., KURTZ, J. B. & WEATHERALL, D. J. (1983). Aplastic crisis due to parvovirus infection in pyruvate kinase deficiency. *Lancet* ii, 14–16.

EDWARDS, J. M. B., KESSEL, I., GARDNER, S. D., EATON, B. R., POLLOCK, T. M., FLECK, D. G., GIBSON, P., WOODROFF, M. & PORTER, A. D. (1981). The search for a characteristic illness in children with serological evidence of viral or toxoplasma infection. *Journal of Infection* **3**, 316–323.

EVANS, JANE P., ROSSITER, MARY A., KUMARAN, T. O. & MORTIMER, P. P. (1984). Human parvovirus aplasia: case due to cross infection in a ward. *British Medical Journal* i, 681.

GERSON, A. A. (1979). Erythema infectiosum (fifth disease). In *Principles and Practice of Infectious Diseases* (ed. G. L. Mandell, R. H. Douglas and J. E. Bennett), pp. 1453–1456. New York: Wiley.

GREENWALD, P. & BASHE, W. J. JR (1974). Epidemic of erythema infectiosum. *American Journal of Diseases of Children* **107**, 30–34.

HAIRE, M. & HADDEN, D. S. M. (1972). Rapid diagnosis of rubella by demonstrating rubella-specific IgM antibodies in the serum by indirect immunofluorescence. *Journal of Medical Microbiology* **5**, 237–242.

HEGGIE, A. D. (1978). Pathogenesis of rubella exanthem: distribution of rubella virus in the skin during rubella with and without rash. *Journal of Infectious Diseases* **137**, 74–77.

HERRICK, T. P. (1926). Erythema infectiosum: clinical report of 74 cases. *American Journal of Diseases of Children* **31**, 486.

ISCHAMER, A. (1889). Ueber ortliche rotheln. *Jahresbericht Kinderheilkunde* **29**, 372.

KELLEHER, J. F., LUBAN, N. L. C., MORTIMER, P. P. & KAMIMURA, T. (1983). The human serum 'parvovirus': a specific cause of aplastic crisis in hereditary spherocytosis. *Journal of Paediatrics* **102**, 720–722.

LAUER, B. A., MACORMACK, J. N. & WILFERT, C. (1976). Erythema infectiosum: an elementary school outbreak. *American Journal of Diseases of Children* **130**, 252–254.

MASON, W. S., ALDRICH, C., SUMMERS, J. & TAYLOR, J. M. (1982). Asymmetric replication of duck hepatitis B virus DNA in liver cells: free minus-strand DNA. *Proceedings of the National Academy of Science, USA* **79**, 3997–4001.

MORTIMER, P. P., TEDDER, R. S., HAMBLING, M. H., SHAFI, M. S., BURKHARDT, F. & SCHILT, U. (1981). Antibody capture radioimmunoassay for antirubella IgM. *Journal of Hygiene* **86**, 139–153.

PATTISON, J. R., JONES, S. E., HODGSON, J., DAVIS, L. R., WHITE, J. M., STROUD, C. E. & MURTAZA, L. (1981). Parvovirus infections and hypoplastic crisis in sickle-cell anaemia. *Lancet* i, 664–665.

PAVER, W. K. & CLARKE, S. K. R. (1976). Comparison of human fecal and serum parvo-like viruses. *Journal of Clinical Microbiology* **4**, 67–70.

RAO, K. R. P., PATEL, A. R., ANDERSON, M. J., HODGSON, J., JONES, S. E. & PATTISON, J. R. (1983). Infection with parvovirus-like virus and aplastic crisis in chronic haemolytic anaemia. *Annals of Internal Medicine* **98**, 930–932.

SERJEANT, G. R., TOPLEY, J. M., MASON, K., SERJEANT, B. E., PATTISON, J. R., JONES, S. E. & MOHAMED, R. (1981). Outbreak of aplastic crisis in sickle-cell anaemia associated with parvovirus-like agent. *Lancet* ii, 595–598.

SHNEERSON, J. M., MORTIMER, P. P. & VANDERVELDE, E. M. (1980). Febrile illness due to a parvovirus. *British Medical Journal* ii, 1580.

SUMMERS, J., JONES, S. E. & ANDERSON, M. J. (1983). Characterization of the genome of the agent of erythrocyte aplasia permits its classification as a human parvovirus. *Journal of General Virology* **64**, 2527–2532.

TEDDER, R. S., YAO, J. L. & ANDERSON, M. J. (1982). The production of monoclonal antibodies to rubella haemagglutinin and their use in antibody-capture assays for rubella-specific IgM. *Journal of Hygiene* **88**, 335–350.

WADLINGTON, W. B. & RILEY, H. D. (1968). Arthritis and hemolytic anaemia following erythema infectiosum. *Journal of the American Medical Association* **203**, 473–475.

WATTS, C. A. H. (1954). Erythema infectiosum. *Lancet* i, 573.