Most human cases have been reported from North America, Scandinavia, Russia, Japan, and the continent of Europe. In Eastern France and Germany there is a zone where human infections have been recognised³ but cases have not been reported before from the French Pyrenees, though infected rodents and hares have been found near Bordeaux.⁴ Our patient's illness thus extends the known geographical distribution of tularaemia, and we report the case as an example of the importation of the disease to Britain.

¹ Ledingham, J C G, and Fraser, F R, *Quarterly Journal of Medicine*, 1923-4, 17, 365.

² Blomley, D J, and Pearson, A D, *British Medical Journal*, 1972, 4, 235.

³ Juszat, H J, in *Welt-Seuchen Atlas Pt I*, ed E Roderwaldt, p 31. Hamburg, Falk-Verlag, 1952.

⁴ Juszat, H J, in *Welt-Seuchen Atlas Pt II*, ed E Roderwaldt, p 37. Hamburg, Falk-Verlag, 1954.

Hereford Hospitals, Hereford

J B WOOD, BM, MRCP, consultant physician
K VALTERIS, FRCPATH, consultant pathologist
R H HARDY, DM, MRCP, senior casualty officer

Department of Bacteriology, Southampton University, Southampton

A D PEARSON, BM, DIP BACT, senior lecturer

Antibody response of infants in tropics to five doses of oral polio vaccine

Three doses of oral polio vaccine (OPV), as currently recommended, are not sufficient for effective immunisation of infants in tropical countries owing to poor seroconversion rates.^{1,2} Consequently paralytic poliomyelitis does occur in vaccinated populations.³ The seroconversion rates of infants to five doses of OPV are reported here.

Subjects, methods, and results

All infants were aged between 6 and 51 weeks when the first dose of OPV was given, by methods described elsewhere.⁴ During the course of investigations the titre of OPV was repeatedly checked and found unchanged from the recommended levels.⁴ The interval between doses was four weeks except in a few children in whom it was five or six weeks. Blood was collected from vaccinees immediately before giving the first dose of OPV, and again four weeks after the third dose, when a fourth dose was given. A third sample of blood was collected four weeks after the fifth dose. All sera were tested for the presence and titre of neutralising antibodies at a starting dilution of 1/8, against 100-300 TCID₅₀ of poliovirus types 1, 2, and 3.⁴

A total of 78 infants were studied. Sera taken from 55 infants after the third dose of OPV were promptly tested along with their prevaccination sera. Thirty-three infants (60%) who had already seroconverted to the three types of poliovirus, and had received a fourth dose, were not given a fifth dose as no further seroconversions were to be gained in them. The remaining 45 infants were given a fifth dose, and four weeks later 21 were found to have seroconverted to all three types. Sixteen had seroconverted to two types only, and six to one type; two infants remained seronegative to three types.

Since the assessment of seroresponse to five doses of OPV would be biased if only the 45 infants were included and the 33 excluded from analysis, all infants are considered together. Among the total of 78 infants studied, 76 (97%) responded to one or more serotypes and 54 (69%) responded to all three serotypes. The type-specific seroconversion rates are shown in the table.

Discussion

Seroresponses of infants and children to one and two doses of OPV, and of infants to three doses, have been described from this laboratory,^{2,4} using similar methods (see table). Obviously there is progressive increase in the seroresponse of vaccinees after each additional dose of OPV after the first. Such a poor seroresponse in the population is due to resistance to vaccine virus "take."⁵ These results indicate that this resistance is not absolute, but could be overcome, in the

Seroresponses of infants and children to one, two, three, and five doses of trivalent OPV

No of doses of OPV	Seroconversion rate (%)			Reference No
	Type 1	Type 2	Type 3	
One	19	61	30	(2)
Two	35	78	48	(2)
Three	69	90	76	(4)
Five	83	96	82	

majority, by repeated doses. Thus five doses are proportionately better than three doses. Some infants remained seronegative to one or more serotypes of poliovirus in spite of receiving five doses of OPV, including two who remained seronegative to all three types of poliovirus. These two had no evidence of immunodeficiency and were clinically normal. They illustrate that the refractoriness to infection and seroresponse may at times be profound and persistent.

On the basis of these results we recommend that the primary course of immunisation for infants in developing countries, especially in the tropics, should consist of at least five doses of OPV given at intervals of four weeks or more.

This investigation was supported by the Indian Council of Medical Research. Help from Ms P Vijayarathnam, I Suresh, and R Elangoven; Dr M Jadhav, Dr L V Devarajan, and Dr L Luther (Vellore); and Dr C W Cockburn (WHO) and Dr John Beale (Wellcome Foundation) is gratefully acknowledged. This study was included in a doctoral thesis submitted to the University of Madras.

¹ Drozdov, S G, and Cockburn, W C, in *Proceedings of the First International Conference on Vaccines against Viral and Rickettsial Diseases of Man*, p 198. Washington, DC, Pan American Health Organisation, 1967.

² John, T J, and Jayabal, P, *American Journal of Epidemiology*, 1972, 96, 263.

³ Ratnaswamy, L, et al, *Indian Pediatrics*, 1973, 10, 443.

⁴ John, T J, et al, *Pediatrics*, 1976, 57, 47.

⁵ John, T J, *American Journal of Epidemiology*, 1975, 102, 414.

Christian Medical College and Hospital, Vellore, Tamil Nadu, India

T JACOB JOHN, MB, MRCP, professor of microbiology and chief, enterovirus laboratory

Induction of labour with buccal prostaglandin E₂

The intravenous and oral routes of prostaglandin administration for labour induction have side effects—notably vomiting, diarrhoea, and uterine hypertonus. In an attempt to obviate these we decided to induce labour by administering prostaglandin by the buccal route. This technique has not been previously reported.

Patients, methods, and results

Labour was induced for obstetric reasons in 24 women at term. Immediately after low amniotomy prostaglandin E₂ tablets were placed in the buccal space between the cheek and the gum above the upper molars. The 0.5 mg tablets were administered according to two schemes. The first 12 subjects received a fixed dose of 0.5 mg every 30 minutes and the remaining 12 an incremental dose that was titrated according to the uterine response—that is, 0.5 mg, 0.5 mg, 1.00 mg, 1.00 mg, 2.00 mg, 2.00 mg every 30 minutes. A maximum dose of 2.00 mg (four tablets) half-hourly was given. Induction was considered successful if 5-cm dilatation of the cervix or delivery was achieved within 12 hours.

In the fixed-dose group 11 patients were successfully induced, as were 10 of the 12 on incremental doses. The table shows the various points chosen for comparing the progress of labour.¹ Shorter mean times occurred in the incremental group. The mean induction-to-delivery times according to parity and cervical state are less in the incremental group, being most defined in primiparous patients with unripe cervixes. Six patients vomited and in one treatment had to be temporarily interrupted. Two cases developed diarrhoea. All the infants were born in good biological condition. Two developed mild jaundice.

Comparison of mean times ($\pm$ SD) taken to reach various labour indices

	Fixed dose	Incremental dose
Induction-IC (min)	27.5 $\pm$ 14.06	10.95 $\pm$ 10.65 (P<0.05)
IC-AC(h)	2.50 $\pm$ 1.39	0.96 $\pm$ 1.16 (P<0.005)
IC-5 cm (h)	3.76 $\pm$ 3.45	2.80 $\pm$ 1.43
IDI (h)	10.21 $\pm$ 6.27	5.25 $\pm$ 2.98 (0.5>P>0.01)

IC = Initial contractions (recorded tocographically).

AC = Adequate contractions (painful).

5 cm = End point of trial.

IDI = Induction-to-delivery interval.

Comment

The buccal route does not have any disadvantages when compared to the oral route of prostaglandin administration. The incidence of vomiting (25%) described for the oral route by other workers is similar.^{2,3} The buccal route also has the advantages of oral drug administration. These are staff convenience and patient comfort, the latter being without the discomfort of an intravenous infusion and the attendant danger of circulatory overload. It may, however, have the added advantage in that the tablet may be removed if uterine hyper-tonus, or any other side effect, maternal or fetal, should occur. Administering prostaglandin E₂ by the buccal route is a satisfactory method for inducing labour at term. An incremental mode of administration is advantageous.

The prostaglandin E₂ tablets were kindly supplied by Dr B S de Wet, Upjohn, South Africa. Dr June Juritz kindly did the statistical tests.

¹ Scher, J, *et al*, *South African Medical Journal*, 1972, **46**, 2009.² Thiery, M, *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1974, **81**, 303.³ Haeri, A, *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1975, in press.

Department of Obstetrics and Gynaecology, University of Cape Town, Cape Town

J SCHER, MD, MRCOG, consultant

P DRYDEN, MB, BS, registrar

D A DAVEY, PHD, FRCOG, professor

Systemic lupus erythematosus and sickle-cell anaemia

In view of the relationship between immunity deficiency states and immune complex diseases such as systemic lupus erythematosus (SLE) a possible association between SLE and sickle-cell disease, in which there is evidence of immunity deficiency, is of interest.

Case reports

Case 1—A 50-year-old Black woman was first seen in 1956 with a six-month history of pleuritic chest pain and arthritis of the fingers, wrists, and elbows. Homozygous sickle-cell disease was diagnosed from alkaline haemoglobin electrophoresis, a positive sickling test, and a characteristic blood film. Levels of Hb A₂ were not measured but were not visibly raised on paper electrophoresis. Haemoglobin was 6.5 g/dl, mean corpuscular haemoglobin concentration 27 g/dl, reticulocytes 13%, and fetal haemoglobin 13%. During the next 10 years she continued to have exacerbations of the arthritis. In 1967 she was readmitted in congestive cardiac failure. Her blood pressure was 150/90 mm Hg, she had spindling of the proximal interphalangeal joints, active synovitis of the wrists, and finger clubbing. Her temperature varied between 37.2°C and 37.9°C. Haemoglobin was 8.8 g/dl, reticulocytes 3.5%, and white cell count 5.6 $\times$ 10⁹/l. The antistreptolysin O titre was normal, serum total protein 68 g/l and albumin 32 g/l, blood urea 7.8 mmol/l (47 mg/100 ml) rising to 17 mmol/l (103 mg/100 ml), ESR 143 mm in 1 h, venereal disease research laboratory test negative. Nine blood cultures were sterile. LE preparations were strongly positive on five occasions. There were many pus cells, occasional red blood cells, and granular and hyaline

casts in the urine. Chest x-ray examination showed cardiac enlargement with diffuse pulmonary infiltration in the lower zones compatible with fibrosis or infiltration. Her fever and arthralgia failed to respond to salicylates. Prednisone 40 mg daily was started, and was increased to 80 mg daily when she became psychotic and had continued fever. It had little effect, and she died suddenly after 10 days. Necropsy showed no evidence of valvular disease or of infectious or Libman-Sachs endocarditis.

Case 2—The patient was a 16-year-old Black girl who had been admitted to hospital 13 times previously, nine of them for pneumonia. When she was 4 months old homozygous sickle-cell disease was diagnosed on haemoglobin electrophoresis at alkaline and acid pH, positive sickle test, and the presence of the sickle-cell trait in both parents. On admission she had a two-week history of jaundice, pleuritic chest pain, and swelling of both knees and ankles. She was jaundiced, had clubbing of fingers and toes, and 18-cm hepatic enlargement. The spleen was palpable. Both knees were warm and contained small effusions. Investigations showed haemoglobin 6.1 g/dl; white cell count 9.1 $\times$ 10⁹/l, 68% neutrophils; prothrombin time normal; electrolytes normal; plasma creatinine 53 μ mol/l (0.6 mg/100 ml), total bilirubin 410 μ mol/l (24 mg/100 ml) (50% conjugated), alkaline phosphatase 53 KAU. Blood and urine cultures were persistently sterile and the serum was Australia antigen negative. Creatinine clearance was 0.9 mmol (100 mg)/min, and urine protein 700 mg/24 h. Antinuclear factor (ANF) tests were consistently positive and DNA binding values (Farr assay) were 50% and 60% (normal 0-30%), C3 was 0.72 g/l (normal 1.2-1.6 g/l). Three days after admission she developed a persistent fever. Treatment with prednisone 60 mg daily was started after 22 days and the temperature fell to normal immediately. She improved clinically and her liver function tests reverted to normal. Six months later she was taking prednisone 10 mg daily, had returned to school, and was clinically well.

Discussion

In each case homozygous sickle-cell disease was diagnosed on adequate evidence. In case 1 five of the American Rheumatism Association criteria for the diagnosis of SLE were met by the presence of pleurisy, arthritis, LE cells, psychosis, and casts in the urine. In case 2 SLE was diagnosed on the arthritis, proteinuria, strongly positive ANF, high DNA binding, and hypocomplementaemia.¹ Although joint symptoms are common in sickle-cell disease these usually arise in the juxta-articular bone and are referred to the joint. The finger clubbing and hepatomegaly in both cases remain unexplained, although an association of gross hepatomegaly and clubbing in sickle-cell disease has been reported.²

The occurrence of SLE in sickle-cell anaemia is of theoretical interest because of the immunological aspects of the two diseases. Johnston *et al*³ have reported a selective abnormality of the alternative pathway of complement activation in patients with sickle-cell disease in whom the C3 and total haemolytic complement (CH₅₀) levels were normal. In studies still in progress we have confirmed this and shown that it is related to a partial deficiency in factor B (glycine-rich B protein), which is a component not only of the alternative pathway but also of the C3_b feedback amplification system.⁴ Such a defect might be partly responsible for the increased susceptibility of sickle-cell patients to infection. Immune complex diseases—particularly SLE—may be associated with genetic deficiencies of various components of complement, and complement deficiency may lead to such diseases through failure to eliminate foreign viral, bacterial, or other antigens. The defect in complement metabolism in sickle-cell anaemia may similarly lead not only to recurrent infection but possibly to immune complex disease.

¹ Hughes, G R V, *British Journal of Haematology*, 1973, **25**, 409.² Konotey-Ahulu, F I D, *Ghana Medical Journal*, 1969, **8**, 104.³ Johnston, R B, Newman, S L, and Struth, A G, *New England Journal of Medicine*, 1973, **288**, 803.⁴ Wilson, W A, Hughes, G R V, and Lachman, P J, *British Medical Journal*, 1976, **1**, 367.

Departments of Medicine and Pathology, University of the West Indies, Kingston, Jamaica

W A WILSON, MD, MRCP, consultant physician and lecturer in medicine
G D NICHOLSON, BM, MRCP, consultant physician and lecturer in medicine
G R V HUGHES, MD, MRCP, consultant physician and lecturer in medicine
(present address: Department of Rheumatology, Royal Postgraduate Medical School, London W12 0HS)

S AMIN, MB, MCPATH, consultant in pathology

GAO ALLEYNE, MD, FRCP, consultant physician and lecturer in medicine

Medical Research Council Epidemiology Unit, University of the West Indies, Kingston, Jamaica

G R SERJEANT, MD, MRCP, head of unit