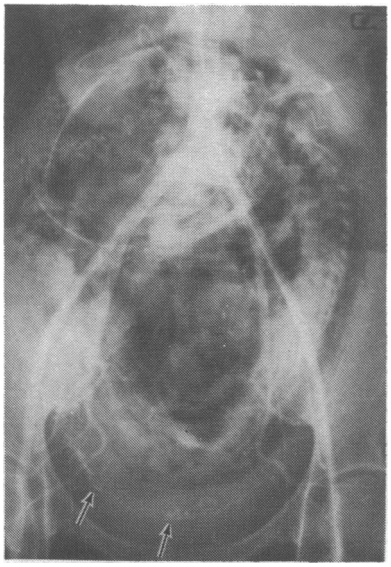

FIG. 3—Arteriogram from Case 3 (anteroposterior view) showing small uterine arteries (arrowed).

escape of about 2 litres of infected liquor amnii and a volume of gas. A subtotal hysterectomy and excision of the sac was performed. The patient was maintained on intravenous fluids and antibiotics and she made a good recovery. She was discharged from hospital after six weeks, and six weeks later she was well.

Cases 3, 4, and 5

These three cases were identical in presentation and were all extrauterine pregnancies complicated by a pyogaseous infection. The pregnancies were all postmature, with subsequent fetal death and failed induction of labour. The radiological findings (Fig. 3) confirmed pyogaseous infections similar to that in Case 2.

Comment

In early cases of gas gangrene or pyogaseous infection of the uterus the features are those of septicaemia, which may lead to circulatory failure and death, as in Case 1. Extension of gas gangrene from the uterus to the peritoneum leads to peritonitis. Other complications are emphysematous vaginitis, thrombophlebitis, lymphangitis, and renal failure (Adams and Adams, 1931; Holly *et al.*, 1960). The principles of treatment are early diagnosis, prompt prophylaxis, early elimination of the focus of infection, massive antisera administration, and systemic antibiotic therapy.

The prognosis depends mainly on the extent and duration of the infection, early diagnosis and treatment, and the degree of kidney damage. Hill (1936) reported a mortality of 63% in 30 cases of postabortal and puerperal gas gangrene.

Russel and Roach (1939) were the first to report the use of *x*-ray examination in the diagnosis of gas gangrene of the uterus. The presence of air and fluid in large amounts, as in the present cases, indicates sepsis by gas-forming organisms, since the gas is more than would be seen in cases of uncomplicated fetal death. Radiography is the diagnostic method of choice. It is quick and reliable, and thus ensures early and prompt surgical intervention to eliminate the focus of infection. Bacteriological examination of vaginal discharge or of a vaginal swab and blood cultures, though useful, may prove negative. Moreover, the results are usually delayed.

We are grateful to Professors J. P. Hendrickse and O. A. Ojo for permission to report these cases, and to Professor S. P. Bohrer for the use of the radiological museum and for his helpful criticisms.

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Aluminium Hydroxide Granuloma

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It is well known that subcutaneous injection of triple vaccine may cause a granuloma, but it is usual for such nodules to subside without treatment after some months. In each of the two cases reported below a postimmunization granuloma was excised before its aetiology was recognized. The histological findings are of interest.

Case 1

On 25 July 1969 a 10-year-old boy presented with a swelling over his right triceps which had been gradually decreasing, but he complained of pain over the nodule and over the scapula. He had had an injection of purified toxoid aluminium hydroxide vaccine on 29 April 1969 and another on 12 June. On examination a firm tender subcutaneous nodule was present over the midpoint of the right triceps. It was not attached to the skin or bone nor inflamed. On excision it was solid, brownish in colour, measured 17 by 11 by 6 mm and appeared to be encapsulated. The cut surface showed a cicatricial centre containing yellowish creamy material (Fig. 1).

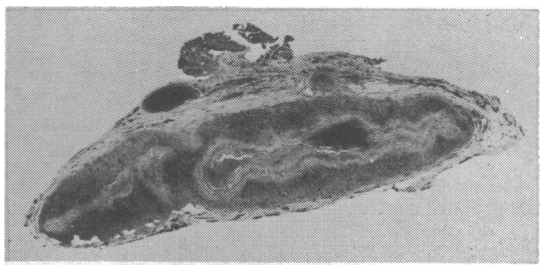

FIG. 1—Naked-eye appearance of a section of the granuloma in Case 1. (H. and E. × 4.)

Haematoxylin and eosin staining showed a centre of eosinophil granular necrotic tissue heavily invaded by polymorph granulocytes. Around the necrotic centre was a narrow zone of epithelioid histiocytes arranged in a loose palisade manner. Many had coalesced to form multinucleated giant cells. Peripherally the histocytes were

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obscured by a dense layer of lymphocytes, plasma cells, and eosinophil granulocytes. The pseudocapsule consisted of compressed collagen fibres infiltrated by inflammatory exudate. Collections of histiocytes and mononuclear leucocytes were also found outside the pseudocapsule. On careful search of several sections deeply basophilic, structureless material was seen in a few giant cells displacing the nuclei to the periphery. The nuclei were usually pyknotic and formed a wreath of rod-like structures outlining the cell boundary. The stored material appeared deep mauve with van Gieson's stain and gave a positive P.A.S. reaction. No iron pigment was present nor were any organisms seen on Gram or Ziehl-Neelsen staining. Aluminium salts were not looked for. Reticulin stain showed destruction of the reticulin fibres in the centre of the lesion. Most of the histiocytes contained P.A.S.-positive material.

Case 2

On 9 January 1970 a 7-year-old healthy girl presented with a small symptomless subcutaneous lump on the outer surface of her upper arm which had been present for about nine months and had been slowly decreasing in size. She had had a triple vaccine booster in December 1968.

On excision the lump (16 by 9 mm) discharged some milky white fluid. Macroscopically it was similar to that in Case 1, but there were important microscopical differences. The central necrotic focus showed no polymorph reaction and there were few lymphocytes and plasma cells. The histological picture was dominated by epithelioid histiocytes and numerous multinucleated giant cells. Many of the latter contained deeply basophilic inclusions which filled the cytoplasm and displaced the nuclei peripherally. The giant cells were mostly elongated or oval, with a frame of pyknotic rod-like nuclei outlining the cell boundary. In the same area there were also many elongated, slit-like or oval empty spaces outlined by rows of rod-shaped nuclei. In some of these spaces remnants of basophilic amorphous material were adherent to the "frame" (Figs. 2 and 3). Much of the basophilic material appeared extracellularly in the necrotic centre.

On van Gieson's staining the stored material was pinkish purple. It gave a positive P.A.S. reaction, and the von Kossa reaction for calcium was negative. Mallory and Parker's haematoxylin method for lead and copper (Culling, 1963) showed light grey granules in the stored material which faded with time. The acid solochrome cyanin method (Pearse, 1960) showed aluminium as a pinkish purple colour, while it was definitely pink by the aluminon method for aluminium hydroxide (King *et al.*, 1955). The physical chemistry department of Glaxo Laboratories detected aluminium hydroxide on *x*-ray crystallography. It was stressed, however, that the concentration was so low that without previous knowledge it might have been missed.

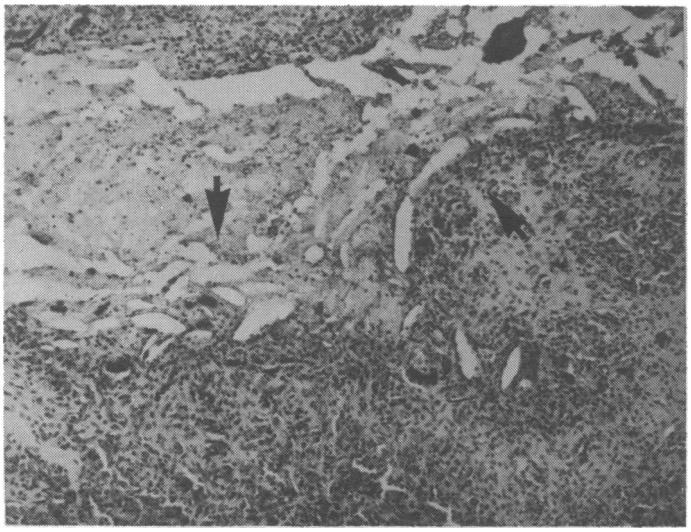

FIG. 2—Microphotograph showing aluminium hydroxide inclusions in giant cells and slit-like spaces outlined by nuclei (arrowed); Case 2. (H. and E. × 160.)

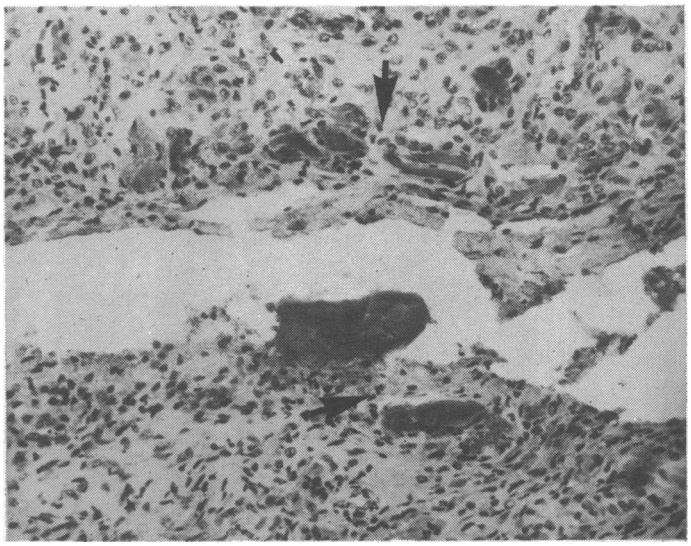

FIG. 3—Microphotograph showing aluminium hydroxide inclusions in giant cells (arrowed); Case 2. (H. and E. × 400.)

Comment

The appearance of the material stored in the granuloma in the second case and the site of the swelling in both cases suggested a metal salt adjuvant used in a vaccine as a possible cause of the reaction. According to information from Glaxo Laboratories (personal communication) the triple vaccine has been combined with aluminium hydroxide adjuvant since 1968 after a gap in its use between 1955 and 1968. Diphtheria and tetanus toxoid have always contained aluminium hydroxide.

We found no British report of excision of a granuloma caused by a vaccine adjuvant. The Medical Research Council's Committee on Clinical Trials of Influenza Vaccine (1955) reported swellings in 14 volunteers out of 399 at three months. The swellings gradually decreased in size. From Sweden, Orell (1962) reported on 15 subcutaneous lesions from the upper arms of healthy patients after mass influenza vaccination. On testing each constituent of the influenza vaccine by inoculating adult guinea-pigs he noted that aluminium oxide adsorbed influenza vaccine produced the characteristic histological appearance, but that it could also be produced by suspension of aluminium oxide in saline with gelatine and phenol (as used in the vaccine) and even by a suspension in saline without any addition. Orell concluded that in the causation of the granuloma the particle size of aluminium oxide was important, since injection of commercial aluminium oxide did not provoke granuloma formation in his experiments.

Voss and Tolki (1960) reported histological findings similar to our cases in a granuloma removed about one year after experimental vaccination with an aluminium oxide adsorbed antiviral vaccine. They claim to have demonstrated aluminium oxide crystals "staining orange with Azan or in the form of Azan-blue-protein complex." Lenz (1966) observed a similar granuloma caused by tetanus toxoid administered by the jet-injection method.

Our two cases are of interest in that conclusive evidence of the presence of aluminium salts was found in one case, and strongly suggestive histological evidence in the other.

We are indebted for the clinical data to Mr. G. F. Walker and Mr. D. M. Forrest, under whose care the patients were admitted. The physical chemistry department of Glaxo Laboratories Ltd., Greenford, Middlesex, performed the *x*-ray crystallography by kind arrangement with Mr. W. J. Watling, of the medical department. Mr. G. Anderson did the histochemical preparations, and Mr. N. G. Le Page produced the photographs.

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Immunosuppressive Therapy in Rh-incompatible Transfusion

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Postpartum injections of 250 μg of anti-D gammaglobulin prevent Rh-immunization of Rh-negative women, with an immunosuppression success rate of approximately 95% (Eklund and Nevanlinna, 1971).

The average fetomaternal transfusion, however, is less than 1·5 ml in 98% of cases (Clarke *et al.*, 1966), and so far there are few observations on trying to suppress primary Rh-immunization due to massive inadvertent transfusion of Rh-positive blood (Hughes-Jones and Mollison, 1968; Keith *et al.*, 1970).

We report here three cases in which Rh-negative women received in error a Rh-transfusion and in which large doses of anti-D gammaglobulin appeared to have suppressed primary immunization when they were tested for immune anti-D formation 12 months or later after the accident.

Case Reports

Case 1.—A 22-year-old primigravida was delivered of a child by caesarean section on 8 March 1968. She was group A Rh-negative and the infant's group was A Rh-positive. A transfusion of 400 ml of A Rh-positive blood was given on 12 March. Five hours later an infusion of anti-D plasma was started intravenously and given in the course of 31 hours. After the infusion of 180 ml over two hours the patient's temperature rose to 38·6°C and she had an attack of shivering. The treatment was stopped for 14 hours and started again at a rate of 30 ml/hour without further reactions. A total of 630 ml of plasma was administered, containing 8,200 μg of anti-D (see Table), as estimated by Dr. N. C. Hughes-Jones. The plasma haemoglobin reached a peak concentration of 150 mg/100 ml. The urinary output was normal throughout. The number of surviving Rh-positive cells was determined by the Ashby differential agglutination technique; the results are shown in the Chart. Samples of blood obtained up to 22 months after the transfusion showed no antibody. At the time of writing the patient had not had a subsequent Rh-postive pregnancy.

Case 2.—An 18-year-old woman aborted at 16 weeks' gestation on 21 May 1969. She had not been pregnant before and had never received blood transfusions. Because of severe bleeding she was given 800 ml of A Rh-positive blood. She was group A Rh-negative. Nine hours after the beginning of the blood transfusion she was given 2,500 μg of anti-D gammaglobulin, and 24 hours later she received an additional dose of 2,500 μg (see Table). Approximate estimates of the survival of transfused red cells were made by an Ashby count; the results are shown in the Chart. On 16 December 1970, 19 months after the transfusion, she gave birth to an O Rh-positive child. Tests for antibody during pregnancy and at the delivery were all negative.

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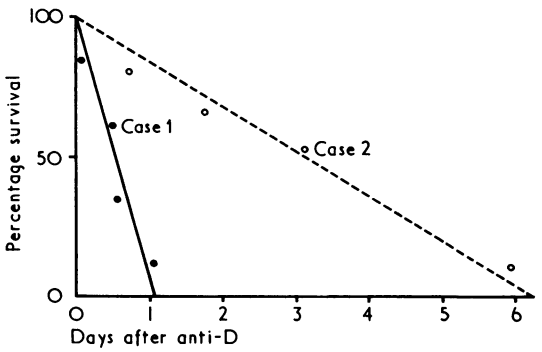
Case 3.—A 21-year-old woman gave birth to her first infant on 27 February 1969. She had not been pregnant before, nor had she required a blood transfusion. Between the second and fifth postpartum hours a transfusion of 400 ml of AB Rh-positive blood was given. Her blood type was AB Rh-negative and her infant's type was AB Rh-positive. Twelve hours later she was given 1,500 μg of anti-D gammaglobulin, followed by a further 1,200 μg at 12-hour intervals. A total of 3,900 μg of anti-D was administered (see Table). Blood samples taken several times up to 12 months after delivery were free of antibody. The patient had not become pregnant as of March 1971.



Estimated survival of Rh-positive red cells in Cases 1 and 2.

Comment

The value of immunosuppressive therapy with anti-D gammaglobulin depends on a knowledge of the risk of immunization resulting from the Rh-incompatible transfusion involved. It has been postulated that a single transfusion of Rh-positive blood stimulates anti-D antibody formation in at least half the subjects (Mollison, 1967). But it appears that if a Rh-negative woman has been transfused with Rh-positive blood a subsequent Rh-positive pregnancy in most cases provokes secondary immune response (Nevanlinna, 1953).

Rh-incompatible large transfusions have been successfully treated in four out of five cases, three of which are presented here (see Table). Though it is not known which of the actual recipients would have been immunized, since only one of them subsequently delivered a Rh-positive child, we have the impression that the rate of immunization must be much higher than one out of five. However, it is possible that a later exposure to the Rh-antigen will still induce a secondary response in the remaining subjects. It is not known how long a delay in the administration of anti-D gammaglobulin is permissible before the possibility of preventing Rh-immunization is missed. There is evidence that anti-D gammaglobulin is effective when giving as late as 72 hours after an injection of Rh-positive cells (Pollack *et al.*, 1969). In all five cases treatment started not more than three days after the transfusion accident.

The disappearance time of Rh-positive cells in Case 1 treated with anti-D plasma was about one day. In Case 2 complete clearance took 6-7 days. The same rate was reported by Keith *et al.* (1970) in one case in which anti-D also did not form. Ninety-five per cent. clearance of Rh-positive cells occurred after 10 days in a case recorded by Hughes-Jones and Mollison (1968), in which the anti-D gammaglobulin failed to prevent